

# Delivering HIV Care and Treatment



## for People Who Use Drugs:

Lessons from Research and Practice

International Harm Reduction Development Program



OPEN SOCIETY INSTITUTE  
Public Health Program



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Lessons from Research and Practice

*Matt Curtis, Editor*

July 2006

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Founded in 1995, the International Harm Reduction Development Program (IHRD) of the Open Society Institute (OSI) works to reduce HIV and other harms related to injecting drug use, and to press for policies that reduce stigmatization of illicit drug users and protect their human rights. IHRD, which has supported more than 200 programs in Central and Eastern Europe, the former Soviet Union, and Asia, bases its activities on the philosophy that people unable or unwilling to abstain from drug use can make positive changes to protect their health and the health of others. Since 2001, IHRD has prioritized advocacy to expand availability of needle exchange, opiate substitution treatment, and treatment for HIV; to reform discriminatory policies and practices; and to increase the political participation of people who use drugs and those living with HIV.

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# Foreword

By Michel Kazatchkine and Joep Lange\*

Much in this volume returns to basic observations. First, AIDS has taught us that prevention efforts gain from the availability of treatment. Second, in many countries, injection drug users (IDUs) are a significant portion of those infected. Third, IDUs—like all people at risk for or infected with HIV—benefit from prevention, treatment, and policies that enable those services.

These assertions would seem uncontroversial. Yet in many countries where IDUs are a significant share of those infected with HIV—in Southeast Asia and China, Eastern Europe and Russia, Central Asia and parts of Latin America—IDU access to antiretroviral treatment is disproportionately low even relative to the limited treatment that is more generally available. Good estimates are difficult to obtain, but trends are easily discernable. In Russia, where 85 percent of cumulative HIV cases are among IDUs, as many as 100,000 people are in need of HIV treatment.<sup>1</sup> Five thousand receive it. In Thailand,

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where rates of injection-driven HIV have continued to climb and where government plans for uni-versal treatment access have more than tripled the number of people receiving ARV since the end of 2003,<sup>2</sup> local NGOs report that there may not be a single active drug user with access to ARV.<sup>3</sup> In a time when universal access is a shared goal, we must ask ourselves why this is so. Is it because of discrimination, lack of political attention, and NGOs not being heard? Or is it also because treatment professionals, uncertain of their abilities to meet the demands already placed on them, have left advocacy on this issue to others?

Certainly there is no reason not to treat IDUs, whose response to treatment is as good as anyone else's presuming they are adherent to the prescribed medicines.

Physicians with experience will tell you that ex-IDUs are among the most compliant patients they know. Active IDUs often have more disorganized lifestyles, but patients who may play Russian roulette with dangerous illicit drugs may still not miss a pill of cotrimoxazole or an antiretroviral. In any event, it is not the physician's role to withhold life saving therapy from someone who needs it, but to create the best circumstances for that treatment to be successful. Even if you succeed in only 20 percent of cases, that is no reason to stop trying. For those patients who succeed, this accomplishment is very important. The history of treatment, or rather, failure to treat, in the developing world offers a warning about the ways that the specter of noncompliance and viral resistance can be used as a pretext to excuse failures of other kinds.

To doctors the world over, IDUs can seem difficult—they are “hopeless,” they are trouble, they take more time. But when you are in an inner city hospital where the patients are drug users, do you have a choice? When you are working in a country where those with HIV are IDUs, would you deny treatment to the majority of those in need? It is amazing that some say a priori that you should not treat; that it is not worth the risk. Withholding life saving treatment for a whole class of people is simply unacceptable from a medical ethical perspective. Moreover, for the individual patient, HIV regimens that fail virologically are generally better for patients than none, since the resulting drug-resistant mutations often weaken the virus and are associated with less rapid immunologic and clinical deterioration. From the perspective of both the individual patients and public health, this of course does not mean that one should not do one's utmost to make sure that patients are adherent to the medicines prescribed.

It has been easier to divide people into the categories of deserving and undeserving than to look carefully at how we might improve services. Some doctors use MEMS caps—pill bottles with electronic devices in the lids—to track when patients take medications, and offer advice or support to those having trouble doing so on time. For IDUs, once-a-day regimens or directly observed therapy may be where hope lies.

Clearly, the practice of medicine for IDUS with HIV is now, as HIV medicine has often been, best conceived as a joint effort of doctors, social workers, and peer educators.

Treatment for IDUs is also a medicine of co-infection. Chapters in this volume attend, rightly, to the particular dynamics of co-infection, emphasizing treatments for those with HIV and tuberculosis, and those with HIV and hepatitis. Longstanding cohort studies among IDUs, such as those from the Netherlands or France, have shown that it is co-infection that often accounts for excess mortality among drug users with HIV, and that attention to the interplay between diseases and the medicines used to treat them is essential. Bacterial infections are also a particular concern for IDUs, as they are in many patients with HIV in Africa.

Recognition of the questions about the treatment needs of IDUs does not resolve theoretical differences about how these are best answered. Some authors in this volume argue for IDU-specific interventions such as randomized clinical trials of prevention technologies or ARV specifically for IDUs, while others of us would prefer to mine cohort studies for lessons already learned to make prevention and treatment accessible to all. In some cases, such as the call for testing of HIV prevention technologies among IDUs, one might ask whether new research is needed. IDUs in France, for example, account for virtually no new HIV infections as a result of widespread access to clean needles and the opiate substitutes methadone and buprenorphine. In Australia, the UK, and elsewhere, infection rates among IDUs have been brought sharply downward. Is it necessary to test pre-exposure prophylaxis (PREP) with antiretroviral agents among drug users? Or might it be more effective to make the technologies we already have available?

In care, too, great claims about the special needs of IDUs, or calls for systems and clinics dedicated exclusively to the needs of IDUs, may mystify as much as they illuminate. Longstanding clinical experience suggests that there is little reason to believe that, apart from co-infections, HIV disease manifests itself differently in IDUs than in others. This is not to say that particular drug users have no specific needs, or that reaching IDUs does not require attention to particular lessons. A chapter in this volume, for example, draws on a cohort study in France to suggest that IDUs on opiate substitution treatment are more compliant with HIV treatment than IDUs who are not. Certainly, given new treatments and new combinations, we do not yet know all we need to know. Administration of interferon-alfa, a hepatitis C medication with severe and complicated side effects, may prove a thornier issue for IDUs than antiretroviral treatment. Where possible, we must identify medical and clinical specificities for IDUs, just as we have learned that in pregnant women we shouldn't use this or that medication, or that with diabetes or liver disease you would not treat with particular agents.

These questions are not simply biological. Cohort studies have also taught us about the value of qualitative research and the importance of asking IDUs themselves how they experience treatment or health care and how that experience might be made better. In the Amsterdam cohort, for example, it became clear that paying drug users was essential to enabling their participation. Some people said it was an unethical incen-

tive, or that we should not provide money to those who would simply use it for illicit drugs. But was the alternative ethical? Leaving people to break into cars to get heroin, get arrested, and interrupt treatment? More generally, we have tended to treat medications as the focus, and failed to invest in behavioral and qualitative research about how they are used and experienced.

Identity politics have long been intertwined with the HIV epidemic. To those who argue in favor of a system able to provide ARV to all on an “intent to treat” basis, others may say that special programs and trials targeting IDUs are more likely to succeed. These are open questions. The essential and unquestionable consensus in this volume, however, is the recognition that drug users are deserving patients rather than a population to be isolated and ignored. The marginalization and discrimination faced by IDUs has had terrible consequences. As these pages make clear, failure lies not only with the patients, but equally, if not more so, with the systems and methods of inquiry that have demanded that all patients be the same. Rather than blaming patients who are different, it is time to demand more creative or committed responses from the physicians on whom they depend.

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Drug use and addiction do not preclude successful HIV treatment.  
If treatment is patient-centered and supported appropriately,  
then it can and will benefit people who use drugs.

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## Introduction

Matt Curtis\*

Injection drug use has been a central feature in the history of the HIV epidemic. Many of the first HIV infections identified in the United States in the early 1980s were among people who injected heroin or cocaine. As HIV spread, hundreds of thousands of people were infected through injection in North America, Western Europe, and the southern cone countries of South America. Today, UNAIDS and others estimate that 10 percent of all HIV infections—and nearly one in three infections outside Africa—are injection-related. By the turn of the millennium, 114 countries had identified cases of injection-related HIV, with HIV prevalence among injecting drug users (IDUs) above 20 percent at sites in 25 countries, and above 50 percent in a further 15 countries.<sup>1</sup> Explosive HIV epidemics among people who inject drugs are still emerging in the countries of the former Soviet Union, China, and Southeast Asia, as well as in parts of India. Injection is also an increasingly noticeable means of transmission in a number of African and Middle Eastern cities.

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While recent developments in HIV treatment have resulted in substantial reductions in morbidity and mortality among persons living with HIV/AIDS, the optimism generated by these advances has been tempered by major concerns regarding inequitable access to treatment.<sup>2,3</sup> Among the groups known to have low rates of access to antiretroviral therapy (ART), and consequently poor HIV/AIDS-related health outcomes, are people who use drugs.<sup>4</sup> Drug users living with HIV have been found to have lower uptake of antiretroviral therapy compared to other HIV-positive persons in a range of settings,<sup>5,6,7,8</sup> and consequently higher rates of AIDS-related morbidity and mortality.<sup>9</sup> The reality is that people experiencing drug use, dependency or addiction are often excluded from the treatment and care they need. As Michel Kazatchkine and Joep Lange observe in the foreword to this volume, the reasons for this are complex: professional training, erroneous clinical exclusionary criteria, comorbid conditions of many patients, and structural barriers such as discrimination, criminalization, and poverty. What is clear, however, is that drug use and addiction do not preclude successful HIV treatment, either in terms of ability to follow treatment regimens or in achieving viral suppression.

Although important gaps in research and debates concerning some interventions remain, the tragedy of injection-driven HIV has prompted research efforts yielding substantial evidence about how best to treat HIV disease among people who use drugs. Medicine can now draw on breakthroughs in our understanding of the natural history of HIV disease, how HIV interacts with other diseases common among people who inject drugs, the influence of sociobehavioral and environmental conditions, drug-drug interactions, and much more. If treatment is patient-centered and supported appropriately, then it can and will benefit people who use drugs.

This volume seeks to address a basic question: Based on available evidence from research and clinical practice, how can medical personnel, public health officials, policymakers, and advocates most effectively provide HIV treatment and related health care for people with a history of drug use? As the international community sets its sights on a goal of universal access to HIV treatment and care, this book is intended to advance the cause of treatment for those who are among the most underserved people living with HIV.

*Delivering HIV Care and Treatment for People Who Use Drugs: Lessons from Research and Practice* follows up and expands on *Breaking Down Barriers*, a report published by the Open Society Institute in 2004. That publication presented a series of case studies documenting successful practice and the evolution of public policies around treatment access for people who use drugs in a number of cities and countries. Although *Breaking Down Barriers* presented examples of successful treatment practice, it was not primarily medical or scientific in nature, rather focusing on the public policy implications of organizing HIV treatment for people who use drugs. The report also restricted itself to HIV treatment, with no attention to such issues as treatment of

hepatitis C, and to issues of injection drug use rather than to non-injecting use of illicit drugs and alcohol.

In contrast, this volume seeks to present information on treatments for HIV and a range of comorbid conditions, such as tuberculosis and hepatitis C, for people who use drugs. Most of the chapters are scientific in nature, and their content has been peer reviewed. Several short chapters examining case examples or the policy dimensions of particular issues are also included. The book is divided into three sections covering some of the major issues faced in organizing HIV treatment with and for people who use drugs. Following these chapters, a section on ethics and clinical research looks to the intersections of HIV prevention and treatment, and the future of research involving people who use drugs.

## Overview

Section one, “Organizing Treatment and Supporting Adherence with People Who Use Drugs,” presents evidence and an overview of strategies for organizing treatment, with a particular emphasis on support for ARV adherence. Patrizia Carrieri and Bruno Spire begin by summarizing the factors influencing adherence both in the general population and among people who use drugs, and put forward evidence-based options for successfully promoting adherence among people who use drugs. The authors observe that “adherence to treatment is a dynamic process,” and that the “predictive approach” dominant among health care providers, which often presumes poor adherence among people who use drugs, is not useful at the individual level. They emphasize the importance of integrating opiate substitution therapies (OST) and other drug treatment, mental health care, peer support, and—when feasible—directly observed therapy, as part of the standard of care for HIV-positive people who use drugs.

Partly in response to concerns about documented suboptimal adherence among active drug users, and especially in light of opportunities for linking ART with opiate substitution therapy (OST) programs, Doug Bruce and Frederick Altice investigate successful models of directly administered antiretroviral treatment (DAART). The authors argue that if programs can be flexibly designed and made user friendly, “DAART can be one of the most effective ways to provide beneficial care to HIV-infected drug users.” When integrated with community outreach, drug treatment and other existing health care structures, DAART can greatly improve adherence among people struggling with addiction or psychiatric comorbidities.

Ralf Jurgens’ examination of prison-based HIV treatment expands on the DAART chapter, while also raising several issues of concern regarding prison-based treatment

access, equality of care between prisons and the community, and post-incarceration continuity of care. Although providing ART in prisons may be challenging, studies have shown that it is feasible, and the scope of HIV infection among prisoners demands greater action. In particular, Jurgens notes that voluntary HIV testing, linked to treatment, should be available to prisoners on entry and afterward, and that administration of these measures by public health authorities (rather than by prison officials) would greatly benefit treatment and care.

As mentioned above, recent increases in international and national funding—though still disgracefully inadequate—have resulted in improved access to HIV treatment in many developing countries with injection-related epidemics. One such country is Russia, where a consortium of NGOs in 2005 initiated a comprehensive HIV prevention and treatment program under the name GLOBUS. Alexei Bobrik, Valeria Letyagina, and Natalia Vasilieva review the first year of the GLOBUS treatment program, which includes a majority of patients with a history of injection drug use. The authors draw lessons from this experience, finding that intensive treatment literacy, peer education, and other methods to support people who use drugs within existing HIV medical structures have retained 95 percent of patients in treatment during the first eight months. However, there are still a number of major barriers to effective treatment in Russia, including a highly vertical medical system that complicates treatment of comorbidities, the “last minute” nature of HIV treatment initiation linked to scarcity of ARVs, and the fact that opiate substitution medications remain illegal in the country.

Shona Schonning’s and Alexandra Volgina’s article describes the experience of Ira, an alcohol and heroin user receiving HIV treatment in St. Petersburg, Russia. The story traces Ira’s history of drug use, how it has impacted her relationship to health care, and her awakening as a peer educator and treatment counselor. Though she continues to drink and use heroin, Ira has successfully found approaches to stay adherent to ARV and improve her health. These experiences, in turn, have formed an important basis for her work in peer support.

“Major Coinfections,” the second section of the book, concentrates on significant infections that frequently affect IDUs such as hepatitis C (HCV) and tuberculosis (TB). Rates of HCV infection are high among most IDU populations, and among HIV-infected IDUs HCV coinfection rates are frequently in the 50–95 percent range.<sup>10</sup> Though not linked to drug injection per se, TB affects a substantial portion of people living with HIV, and IDU populations are often at higher risk of TB infection related to homelessness, incarceration, and other factors. In Ukraine, TB is responsible for 50 percent of HIV-related mortality, with a similarly dire picture in a number of other countries. Among countries with substantial injection-related HIV epidemics, HIV prevalence among TB patients exceeds 10 percent in Cambodia, Thailand, Burma, parts of India and Ukraine, and elsewhere.<sup>11</sup> Both illnesses are life threatening in their own right, and both may affect

HIV treatment by altering disease progression, limiting treatment options because of drug interactions, or through other factors.

The section begins with a study of the natural history of HIV/Hepatitis C (HCV) coinfection by Gail Matthews and Greg Dore. While acknowledging the difficulties of developing natural history studies of HIV/HCV coinfection, Matthews and Dore state that HIV clearly accelerates HCV disease progression—a major issue for any program treating people infected by HIV through injection drug use. Whether HCV in turn affects HIV disease progression cannot be definitively concluded based on research to date, though some evidence indicates that coinfection may affect CD4 count recovery after ART initiation. Importantly, Matthews and Dore show that HIV/HCV coinfecting persons, including IDUs, do benefit from ART in terms of virological and immunological response and a likely reduction in liver disease progression.

The chapter by Lynn Taylor, Beth Schwartzapfel, and Pierre Gholam reviews prevention and treatment options among HIV/HCV coinfecting persons, and examines models of clinical practice in which management and treatment of HCV infection is accomplished alongside HIV care. “Given the large numbers of coinfecting IDUs worldwide,” the authors conclude, “the question of whether to address HCV in HIV-coinfecting IDUs is moot.” Preventing further HCV transmission and slowing disease progression through measures including reduction of alcohol intake and vaccination for hepatitis A and B is highly feasible. Treatment, though often difficult, greatly benefits from comprehensive medical care that simultaneously addresses HIV.

Finally, Phillipp du Cros and Adeeba Kamarulzaman review tuberculosis (TB) in the context of HIV infection, with attention to diagnostic and treatment issues relevant to coinfection. Du Cros and Kamarulzaman note the effect of immunosuppression in reducing the accuracy of some TB diagnostics, and that extrapulmonary TB is more common among HIV-coinfecting patients. Treating TB in HIV-infected patients presents several challenges, including a large number of medications which may complicate adherence, interactions between ARV and TB medications, and questions of when to initiate or discontinue HIV treatment in the presence of TB. In addition, some TB medications interact with OST, or are hepatotoxic, constraining their use in HCV-coinfecting patients.

The book’s third section, “Drugs, Alcohol, and Antiretroviral Medicines,” collects available evidence on interactions between ARVs, street drugs, OST medications, and alcohol that may impact HIV treatment. The chapter by Alice Lin-in Tseng and Tony Antoniou is a comprehensive overview of drug-drug interactions. Much is known on this subject that may assist doctors, despite the fact that most information is derived from *in vitro* experiments, case reports, and animal studies—a limitation which highlights the urgent need for new interaction studies. Possible drug interactions can be managed in many instances. However, Tseng and Antoniou note that “given the ris-

ing incidence of HIV infection among substance users and the increasing use of complex combination antiretroviral regimens, the risk of adverse drug interactions with possibly fatal consequences cannot be overlooked or ignored.” They recommend that medical staff should routinely gather comprehensive medication histories including on the use of illicit drugs, while striving to ensure confidential, nonthreatening and nonjudgmental treatment of the information. Ultimately, because of the multiple interactions of illicit drugs with combination ART, it may often be more medically feasible to develop strategies to reduce or eliminate illicit drug use than to alter HIV treatment regimens.

Further exploring this subject in terms of research, Mauro Guarinieri and Tracy Swan write that ARV manufacturers have failed to either provide available data on illicit drug-ARV interaction to doctors and patients, or to conduct relevant studies. As a result, in effect “HIV-positive drug users are forced to conduct uncontrolled, one-person experiments, often on a daily basis.” The framework for moving ahead is clear, as indicated in the U.S. National Institute on Drug Abuse publication, *Recommendations for Future Research*. Guarinieri and Swan call on regulatory agencies in the United States and Europe to press for complete drug interaction information that will benefit HIV patients who use drugs.

Jon Levinson and Jay Dobkin write on the effects of alcohol use and misuse on HIV disease and treatment. Often overlooked, alcohol misuse is a common condition among people who use illicit drugs, and lifetime rates of alcoholism among all PLWH have been found to exceed 10 percent in many study populations. Most notably among PLWH with a history of injecting drug use, Levinson and Dobkin describe the major risks of alcohol use and HCV-related liver damage, especially among women, who typically have more rapidly progressing liver disease. Moreover, heavy alcohol consumption has been shown to decrease the response to interferon, reducing the likelihood of successful HCV treatment. The authors also examine the correlation between alcohol misuse and poor ARV adherence, and review treatment options for alcohol dependency.

“Ethics, Clinical Research and Drug User Involvement,” the final section of the book, centers on the tensions between the need for new research that will benefit IDUs at risk of or infected with HIV, and the need for human rights protections within research programs involving such marginalized and abused populations. The authors in this section seek to answer two key questions: How can research be organized in a way that is clearly ethical as well as scientifically and financially feasible? And how can people who use drugs and their advocates most effectively be involved in representing community interests among researchers and donors?

Konstantin Lezhentsev, Mauro Guarinieri, and Daniel Raymond use their chapter to examine the common exclusion of people who use drugs in clinical trials of HIV treatment medicines. The relative dearth of research on HIV treatment among people

who use drugs has resulted in numerous areas in which clinicians and people who use drugs may not have accurate information relevant to their treatment. The authors state that studies examining ART among IDUs have already yielded important information for tailoring clinical guidelines to the needs of IDUs. According to them, these studies are a “compelling argument for broader inclusion of drug users in HIV clinical research to provide a better characterization of the relative benefits and risks of treatment.” Moreover, failure to enroll active drug users in clinical research “supports the reluctance, or unwillingness, of treating physicians to prescribe ARV to drug users.”

In the next chapter, Karyn Kaplan presents a case study of recent debates surrounding the tenofovir HIV prevention trial currently underway in Thailand. Recognizing the importance of such research and its potential to save lives in the future, Kaplan writes that researchers and donors are nonetheless still bound by ethical standards, in this case the need to provide a complete package of HIV prevention options for the particular population (IDUs) in the placebo controlled study. The piece documents efforts by the Thai Drug Users Network and allied organizations to constructively engage with researchers and ameliorate the community’s concerns regarding the ethical treatment of study participants.

Chris Beyrer furthers this discussion in the last chapter by scrutinizing the balance between HIV prevention trials and research ethics in locations with poor access to standard prevention measures—especially sterile syringe provision for IDUs. The central challenges, Beyrer writes, are that research with IDUs “faces ethical hurdles in providing evidence-based prevention services when these are politically fraught,” and “human rights challenges when trials occur in settings where rights violations of IDUs are common.” Determining that scientific and political reasons currently make HIV vaccine trials among IDUs only feasible in high-incidence settings, Beyrer proposes a “skillful means” approach that builds strategic alliances to diffuse conflict between donors, researchers, and community advocates, and finds ways to address the concerns and limitations of each side.

## Complete Care for People Who Use Drugs: Outstanding Challenges

Though *Delivering HIV Care and Treatment for People Who Use Drugs* attempts to cover the major issues related to HIV treatment and drug use, some important topics have not been covered in chapters in this volume. Mental illness, for example, may impede individuals’ ability to comply with ARV regimens, and affect other areas of health, housing stability, or security which themselves may disrupt HIV treatment. Many countries fail to provide satisfactory palliative care and pain management to active IDUs and people

on opiate substitution therapy, especially in countries where the concept of palliative care is not well-developed. Stigma and discrimination, the absence of basic knowledge about pain management in IDUs, and fears of “medical addiction” are also considerable barriers to relieving the suffering of these patients. In addition, greater consideration must be paid to the quality of treatment for substance dependence, new research on substitution therapy for stimulants,<sup>12</sup> and harm reduction measures for stimulant users, who comprise a substantial portion of IDUs. Finally, IDUs often face infections, including abscesses and endocarditis, and hazards such as drug overdose that can adversely affect HIV treatment and health care.

These problems speak to the need to integrate HIV treatment, drug dependence treatment, and primary care with harm reduction services, either on-site or through case management and referrals. Harm reduction programs can directly support HIV treatment through patient outreach, case management, and community education. Many harm reduction programs also address immediate crises in housing, food, and health care, thereby supporting longer-term interventions including HIV and drug treatment. Several countries with significant injection-related HIV epidemics have had great success with this approach, notably Brazil which has incorporated harm reduction services into its HIV treatment system for many years.<sup>13</sup> Other countries such as Ukraine and Russia are now organizing HIV treatment in concert with harm reduction services under new Global Fund-supported programs.

While this volume focuses on the medical, it is essential that health care practitioners do not lose sight of the political. Inevitably, politics intrudes on any discussion of drug use and appropriate responses. Many of the chapters allude to the dominant view of people who use drugs as undeserving criminals and their disenfranchisement from health services. Many of the conditions undermining the ability of people who use drugs to engage in or help to shape medical care—including lack of adequate housing and employment, lack of drug treatment or mental health care, and fear of arrest—reflect the policies determined by law enforcement authorities. The intersection of policy and health must be continuously examined if the promise of universal access to HIV treatment, or other critical forms of treatment, is to be realized.

## A Summary of Global Lessons Learned

Based on the evidence reviewed in this book, and with particular attention to developing countries where the great majority of injection-related HIV infections occur, the following recommendations should be considered with regard to how treatment challenges for people who use drugs may be best addressed.

- ▶ **Make Treatment and Care Available for All.** Although drug use may complicate HIV treatment, it is a challenge which can be overcome. Drug use in and of itself is neither a legitimate reason to exclude people from HIV treatment and care nor a predictor of treatment failure. Drug use must be seen for what it is: a health issue. Discrimination, whether based in culture or in drug policy, has no place in medicine. A priori criteria that exclude people who use drugs from treatment should be removed. Treatment protocols should detail effective treatment options for people who use drugs, and medical personnel must be educated on drug use and addiction, co-infections common among IDUs, and possible drug-drug interactions.
  
- ▶ **Establish Flexible Treatment Support Services.** For people struggling with drug dependency and related comorbid conditions, a number of effective, low-cost options are available to support ARV adherence and overall treatment success. In addition to the drug treatment therapies addressed below, HIV treatment programs should consider a range of possible interventions, including peer support and peer-based treatment education and patient advocacy, and case management and social services. It is critical that people who use drugs have meaningful involvement in designing, implementing, and evaluating such programs and services. When poverty, homelessness, psychiatric comorbidity or other conditions make it difficult for patients to take charge of their own treatment, directly administered antiretroviral treatment (DAART) programs should be considered. However, especially in the case of DAART, it is essential that support programs maintain the flexibility to recognize and respond to changes over time in a patient's drug using behavior and his or her ability to effectively manage treatment with or without structured support.
  
- ▶ **Provide Effective Drug Treatment on Demand.** Given the global prevalence of drug use, including alcohol, all countries, especially those with injection-related HIV epidemics, must rapidly expand access to the most effective available drug treatment modalities. For opiate dependent persons, no treatment has been shown to be more effective than the use of substitution medications, including methadone and buprenorphine. Legal restrictions limiting their use for drug treatment should be removed wherever present, and governments should establish patient-friendly treatment protocols and adequate training for medical personnel. Alongside opiate substitution therapy programs, a full range of medication-assisted and drug-free treatment programs for drug and alcohol dependency should be made available on demand, and integrated with HIV treatment programs through strong referral systems or on-site services.

- ▶ **Integrate Medical and Other Care.** Many countries are failing to utilize existing medical and public health resources for HIV treatment to support people who use drugs. Integration of HIV treatment with tuberculosis, hepatitis and other infectious disease treatment, mental health care, harm reduction services, and drug treatment must be prioritized. As a means of making HIV treatment and related health care as accessible as possible, health authorities should strive to incorporate treatment into primary health care as much as possible. Coordinating HIV treatment with harm reduction services holds particular promise for improving both HIV treatment and prevention, including through the use of harm reduction-based patient outreach, peer support and education, case management, antiretroviral treatment programs, and other services.
  
- ▶ **Address Viral Hepatitis as a Component of HIV Treatment and Care.** Better attention must be paid to hepatitis B and C infection, which affects an estimated 200 million people<sup>14</sup> and as many as 90 percent of injection drug users in some locations.<sup>15</sup> In all cases, viral hepatitis status should be assessed following an HIV diagnosis and regularly throughout the course of HIV treatment and care. Liver health should be a central component of HIV treatment plans, hepatitis B vaccination should be routinely provided to injection drug users, and all possible steps should be taken to reduce the likelihood of HCV-related liver disease progression. Where available, options for HBV and HCV treatment should be considered in light of HIV disease status, mental health, and other factors. Given the global prevalence of viral hepatitis, price reductions for medications used in hepatitis treatment are urgently needed, as is registration in all countries where medications are not currently available.
  
- ▶ **Guarantee Access to HIV Treatment for Prisoners.** Repressive drug laws have led to the incarceration of hundreds of thousands of injection drug users. Because of this, and the fact that drug use and sex continue in virtually all prisons, incarceration has been associated with HIV incidence, and many prisons have much higher HIV prevalence than the broader community. Yet HIV treatment and other health services are failing in many prison settings. Governments must guarantee that prisoners receive HIV treatment and related health care equivalent to that available in the community, and that treatment is managed by health agencies, not corrections officials. There is no evidence indicating that prisoners are less able to succeed in treatment. When incarcerated, people living with HIV must not be quarantined or provided health care in a manner that compromises their confidentiality or otherwise infringes on their rights. Finally, given that incarceration has been associated with high rates of HIV

treatment discontinuation among people who use drugs,<sup>16</sup> prison HIV treatment programs must establish links to their community-based counterparts in order to ensure continuity of care.

- ▶ **Disseminate Existing Evidence on Drug Interactions and Promote New Research.** Interactions between antiretroviral medications, street drugs, and opiate substitution medications pose a substantial danger to people who use drugs and who are receiving HIV treatment. Interactions may undermine the efficacy of treatment and medical personnel and patients must be educated on common potential interactions, notably those involving protease inhibitors and non-nucleoside reverse transcriptase inhibitors that can affect the enzyme systems also responsible for metabolizing many illicit drugs. Clear and specific information on interactions must be included on drug packaging. Clinical research to more thoroughly understand drug interactions in vivo is needed in order to promote the safe use of antiretroviral medications for all populations in need of treatment.
  
- ▶ **Promote Voluntary HIV Testing and Counseling Targeted to IDU Communities.** In many countries with injection-related HIV epidemics, huge disparities exist between the number of documented HIV infections and total estimated cases. This problem has been well known for many years, yet some countries such as Russia have even curtailed testing in the face of explosive epidemics. Public health agencies must promote voluntary HIV testing targeting injection drug users and other populations at highest risk of infection, offer them respectful counseling, and guarantee anonymity. In light of expanding access to ART in the developing world, low threshold availability of testing is a basic step in reorienting treatment away from last-minute emergency care toward chronic disease management. At the same time, policies often linked to law enforcement practices that force people who use drugs to be tested or publicly reveal their HIV status must be eliminated.
  
- ▶ **Ensure the Participation of People Who Use Drugs in the Design and Conduct of Treatment and Research Programs.** A fundamental principle of good medical practice is that patients must be informed participants in decisions affecting their treatment and health. At the community level, expert consultation with advocates representing people who use drugs can lead to more informed, better functioning treatment programs. Evidence from various settings shows that involving people who use drugs in program delivery can lead to better coverage of programs and increased contact with those most at risk for poor health outcomes.<sup>17, 18, 19</sup> In the area of clinical research, it is imperative that authentic community review is a central feature of research design. Peer educators, patient advocates, and outreach

workers should be employed, trained, and empowered to participate in the design and management of HIV treatment programs. Clinical trials of HIV prevention or treatment technologies involving people who use drugs must fulfill the spirit, as well as the letter, of the World Medical Association's Declaration of Helsinki. Clinical trials must also be subject to genuine community ethical review and be conducted as ongoing partnerships between communities and researchers.

# 1. Organizing Treatment and Supporting Adherence With People Who Use Drugs



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When engaged in stable care with an experienced staff and adequate support, IDUs can adhere to HAART and have outcomes equivalent to non-IDU patients. Ongoing drug use is therefore not a valid criterion for denying active IDUs access to HAART.

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# Adherence to Antiretroviral Treatment in HIV-Infected Drug Users: The Role of Psychosocial Factors and Opiate Substitution Therapy

Patrizia Carrieri and Bruno Spire\*

## Introduction

Currently, an estimated 10 percent of all new HIV infections worldwide can be attributed to injecting drug use. Relatively recent HIV epidemics in Eastern Europe and Central Asia have been largely driven by injecting drug users (IDUs). In Eastern Europe, several states of the former Soviet Union—Estonia, Russia, and Ukraine—appear to have the largest and most widespread epidemics. HIV prevalence related to injection drug use

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has also risen dramatically in China, Indonesia, Iran, Myanmar, North Africa, the southern cone of Latin America, and Vietnam. These epidemics in IDUs are characterized by an explosive growth as documented in some studies showing that HIV prevalence among IDUs has risen considerably in the last few years [1]. In addition, in many Eastern European and former Soviet Union countries such as Russia [2], HIV infection is rapidly moving from IDUs to both heterosexuals through the so-called “bridging groups” such as sex workers, and to children through vertical transmission.

Highly active antiretroviral treatment (HAART) was first introduced in 1996 in Western countries and has brought about a revolution in the course of HIV disease, bringing dramatic reductions in the occurrence of opportunistic infections and mortality. HAART efficacy, however, requires a high level of patient adherence to the prescribed regimen, which to date means maintaining a lifelong prescription. In addition, these treatments are often accompanied by a considerable number of side effects that can compromise the patient’s quality of life [10].

Most long-term studies of HIV-positive people in the pre-HAART era found no difference in the progression of HIV to AIDS and death between those who use illicit drugs, including the injection of heroin and cocaine, and non-drug users. In the HAART era, there is still no evidence that IDUs have a faster progression of their HIV disease. A study of 640 women published by Rompalo and colleagues [11] showed that, over seven years, there was no difference in progression between the women who had past, current, or no history of injection drug use. If any difference in progression was observed between people infected with HIV through injection drug use and other HIV transmission groups [12], it was more likely attributable to the higher prevalence of other comorbidities (such as hepatitis), to problems of nonadherence to HAART in IDUs, or to a delay in access to HAART.

## Access to HAART for IDUs

Active IDUs have often experienced delays in access to treatment, especially in the early phase of HAART [13]. In some cases, the delays were mainly due to physicians’ perceptions about how IDU patients would follow prescriptions. In other cases, delays could be attributed to guidelines for treatment provision that suggest starting treatment only when a patient has entered a “routine” where his/her opiate dependence is also treated [14]. Yet little is really known about why drug users refuse to take medication and whether this is related to fear about dangerous interactions between HIV medications and illicit drugs and alcohol. Given equal access to care, IDUs are often less likely to have undetectable viral loads, suggesting other barriers exist to successful treatment. When

IDUs are successful in achieving durable undetectable viral loads, they experience the same positive clinical impact as non-users [15].

## Adherence and HIV Progression

In the pre-HAART era, sociobehavioral studies mainly focused on injecting drug use and sexual behavior that risked HIV transmission. With the introduction of HAART, attention has focused on new sociobehavioral questions, the most crucial of which is adherence to the prescribed regimen.

Adherence is critical because poor compliance with a treatment regimen may lead to virological failure and the emergence of resistance that may lead to a change of the regimen and the reduction of the number of treatment strategies potentially available. Lack of adherence is also associated with clinical progression of HIV disease [16–18] and mortality [19]. In addition, optimizing adherence in the early months of HAART (4–6 months) is crucial to ensure long-term immunovirological success. Moderate deviations from high adherence (88–99 percent) during follow-up (maintenance phase after 6 months) have less negative impact on viral replication [20].

Possible development of drug-resistant HIV due to poor adherence has frequently been used as a rationale for excluding IDUs from HIV treatment. Indeed, since the beginning of the HAART era many have speculated that poor adherence was the major cause of viral resistance [3;4]. In fact, the real issue is achieving viral suppression, rather than adherence to medications per se. Among treated patients who do not achieve full viral suppression by HAART, patients with relatively high but imperfect adherence (c. 80–95 percent) are more likely to develop drug resistance than those attaining >95 percent adherence or those with very low adherence [5;6;7]. Of course, although poorly adherent patients appear to be less at risk to develop drug resistant HIV mutations, they are at much greater risk of failing to achieve viral suppression, with consequent negative health outcomes. Clinicians should focus on supporting near-100 percent adherence in all patients, regardless of drug using history, because it is the only reliable means of achieving both viral suppression and reduced risk of drug resistance.

These reasons make the identification of factors to predict adherence among IDUs critical not only for HIV providers but also for all health care providers of HIV-positive IDUs. The literature in this field is extremely rich, but we can classify major results according to a modified version of Ickovics' classification [21]:

- ▶ Pretreatment characteristics: age, gender, current IDU status, injection career, opiate substitution treatment (OST), alcohol consumption, substance abuse or misuse;

- ▶ Psychosocial factors: patient-provider relationship, depression, anxiety, social support, self efficacy; and body image;
- ▶ Patient’s experience during treatment: self-reported side effects, change in substance or alcohol use during treatment, incarceration;
- ▶ Treatment related characteristics (medication regimen complexity, pill burden, dosing frequency, dietary instructions, type of combination, and management of medication side effects).

## Factors Associated with Adherence in the General Population of HIV-Infected Patients

Among fixed determinants, high social status (expressed by income, education, history of drug abuse, comfortable housing or other social vulnerability indexes) [22–25] has been reported to be related to high adherence to antiretroviral treatment. The pattern of factors associated with adherence also varies according to gender [26]. Among psychosocial factors, specific aspects of the patient-provider relationship such as patients having a positive perception of their provider’s competence, as well as the levels of trust, open communication, and inclusion in decision-making between patient and provider [27;28] are all significantly related to high adherence, and improving the different aspects of this relationship may enhance adherence. These aspects and other factors reveal adherence to treatment as a dynamic process that can be difficult to predict and can vary widely over time [29;30].

Despite the dynamic nature of adherence, a “predictive approach” to identifying adherent patients still predominates among health care professionals. This approach can either lead to various interventions for “correcting” non-adherent behavior or, in some cases, provide justification for denying treatment to certain patients. An alternative “empathic” approach aims instead to support all patients on HAART during treatment. This approach puts more emphasis on providers considering the patient’s subjective experience as a major factor in determining adherence. A study was carried out by our team using data from the APROCO cohort aimed at understanding the validity of predicting non-adherent behavior and identifying “high risk” patients on the sole basis of simple socio-demographic characteristics. This study showed that when factors associated with adherence in a longitudinal way and pre-treatment issues and patients’ experience during treatment are considered, then self-reported side effects, changes in psychosocial factors (depression, support), addictive behaviors, and opinions about efficacy can play a major role in determining non-adherence behaviors [30]. The role of self-reported side-

effects on medication adherence has been confirmed by several studies [31;32]. Another study based on APROCO longitudinal data has shown that a patient's perception of body modification (self-reported lipodystrophy) is associated with adherence failure [33].

Another means to better assess adherence potential is by examining patients' self-efficacy outcome expectations. Patients whose a priori negative judgments about HAART are confirmed, as well as those who form negative judgments during their first months of treatment, are more likely to be non-adherent. Conversely, those patients who formed positive judgments about HAART during treatment tend to be as adherent as those whose a priori positive judgments were maintained [31]. Other studies consistently confirmed these results: self-efficacy was found as the most important predictor of adherence [34] while Kerr et al. [35] have found that adherence efficacy expectations are predictive of high adherence and negative outcome expectations are associated with non-adherence.

The presence of depression can also be a key factor influencing HAART adherence. Several studies have demonstrated that depression is associated with reduced adherence in the general HIV population [31;37] and that it is a significant predictor of HIV clinical progression [38;39], even during the maintenance phase of HAART when a routine approach to taking medication should have already been adopted [40].

The role of social support in helping patients adhere to their regimen is another important consideration. Berg [26] has found that social support is associated with increased levels of adherence among men. Recent results on a five-year evaluation of adherence by Carrieri [40] showed that a patient's adherence behaviors may improve when they receive strong support from their main partner even during the maintenance phase of HAART. A study from Gonzalez et al. highlighted that greater social support and a positive state of mind are both related to better adherence and that a positive state of mind mediates the relationship between social support and adherence in HIV positive populations [41].

Changes in the frequency and complexity of treatment regimens may also influence adherence. While inconsistent results were found regarding the number of daily pills and poor adherence (as there have been few studies documenting this relationship, [42–44], complex regimens based on three or more intakes per day are associated with lower levels of adherence [45]. Currently, most regimens have reduced these burdens. A recent study, however, could not give any evidence that once a day regimens were associated with better adherence than BID (twice a day) regimens [40].

On the whole, these results pertaining to general HIV-infected populations confirm that it is difficult to predict adherence a priori and that time-varying factors related to patients' experience during treatment are the best predictors of a patient's ability to adhere to HAART.

## Factors Associated with Adherence in IDUs

Although numerous studies of injection drug use and HAART adherence sometimes appear to offer conflicting results, the most important consideration is that many individual, social, and structural factors influence adherence. With a range of appropriate adherence support measures—including OST and other drug treatment, peer support and education, and careful consideration by medical personnel of each patient’s needs and capabilities—both current and former injection drug users are in fact able to achieve high levels of adherence to HAART.

Ongoing drug injection has been found to be associated with non-adherence [25; 46;47] or with adherence failure [48] in a number of studies, as well as other addictive behaviors such as elevated alcohol consumption [47;49] or cocaine use [50]. More specifically, Bouhnik et al. [25] found that for individuals who remain opiate dependent, ongoing drug injection is predictive of non-adherence. By contrast, among those who are no longer opiate dependent (i.e. ex-IDUs not on opiate substitution treatment), social vulnerability is the only factor explaining non-adherence. This last result confirms that the common perception that “drug users do not adhere to HAART” may hide the confounding effects of poverty, psychiatric morbidity, and poor patient-physician relationship that characterise many drug users’ lives. Like the general population, physicians often have negative attitudes about substance users, making it difficult to develop deep, beneficial patient-provider relationships.

These perceptions are likely contributors to decisions to delay access to treatment for IDU patients until they enter a routine schema to properly follow prescriptions [43; 51]. HIV and non-HIV health care providers are often not fully equipped to care for substance users because many medical schools provide little education about drug use and addiction. Exacerbating this problem is the higher propensity of more vulnerable patients to use the emergency department as a substitute for primary care [52].

An analysis made using data from the MANIF 2000 cohort, a sociobehavioral cohort started in 1995 [53], focused on the identification of factors associated with adherence to HAART after four months of treatment.

Moatti et al. studied the influence of buprenorphine substitution treatment on adherence to HAART. Multivariate analysis confirmed that active IDUs were about five times more likely to be nonadherent than IDUs on OST and ex-IDUs. Furthermore, IDU patients on OST appeared to have somewhat higher levels of adherence than ex-IDUs, though this difference did not reach statistical significance after adjustment of other cofactors.

In examining the practice of buprenorphine delivery in France, several interpretations can be made to explain the success of buprenorphine substitution therapy in supporting better adherence to HAART. Firstly, buprenorphine stabilizes the social

situation of opiate using individuals. Indeed, buprenorphine prescription can be initiated and followed by any medical doctor, leading to easier access to this medicine. Second, the patient must attend weekly appointments at the doctor's consulting room. Furthermore, the physicians who are involved in buprenorphine prescription work in networks with social workers, pharmacists, and other health care workers, that can offer social support and increase adherence. In this context, physicians tend to consider the multiple issues concerning the patient, including negative life events, and this understanding can help the patient's willingness to be treated for HIV, as well as for drug addiction.

A Canadian study has reported methadone use was associated with HAART receipt but that it did not improve adherence [54]. However, in this study, the evaluation of adherence was performed after 30 days of HAART, and it is possible that this early evaluation does not offer the patient a real opportunity to establish a routine. By contrast, in centers where methadone is administered locally and on a daily basis, together with antiretroviral treatment (direct observation treatment), total adherence is expected for patients who are also adherent to methadone provisions [55]. However, levels of non-adherence while on methadone treatment are comparable to estimates from other chronic diseases [56]. On the other hand, some interactions between methadone and some antiretroviral treatments such as nelfinavir require increased doses of methadone to obtain efficient OST [57].

An analysis using data from the MANIF 2000 cohort [48], focused on the identification of factors associated with adherence failure occurring within the first 18 months of HAART among patients who were initially adherent. Each episode of non-adherence during follow-up was defined as an "adherence failure" event. Adherence evaluation at follow-up visits revealed that a quarter of patients experienced adherence failure over the first 18 months. Adherence failure was mainly explained by the lack of a stable relationship, depression assessed by the CES-D score, and report of any kind of injection—most frequently, cocaine or buprenorphine. Ongoing injection (whether continued or as a result of relapse) is a strong predictor of adherence failure. These results underline the need for closer and more adequate monitoring of patients enrolled in substitution programs. Injection during buprenorphine treatment constitutes a failure of the substitution treatment and suggests either the need for higher dosages (sometimes required due to interactions between buprenorphine and other antiretroviral treatments) or inadequate services to polydrug users, especially cocaine injectors. Consequently, there is a need for either reinforcement using other additional psycho-cognitive approaches, or a switch to other forms of OST such as methadone. Together with ongoing injection, the lack of a stable relationship is associated with an increased risk of adherence failure. In HIV-infected IDUs, other studies have confirmed that depression may increase the risk of poor adherence to treatment [30;58].

IDUs have a high prevalence of psychiatric comorbidities and depressive symptoms. One study of MANIF 2000 cohort participants showed that depressive symptoms represent the second highest cause of hospitalization, after opportunistic infections [59]. Depression needs to be diagnosed in a timely manner and properly treated in order to maintain adherence to HAART.

A recent approach that is being highly promoted is a screening for depression and provision of adequate treatment at the initiation of HAART. These measures could have a major impact not only on adherence, since treating depression in HIV-infected individuals may enhance adherence [60;61], but also on clinical progression. Indeed, depression in IDUs has also been found to be a determinant of clinical progression independent of adherence [17].

An appropriate management of perceived side effects, which in the case of drug users are also related to pain management problems, could improve adherence and reinforce the patient-provider relationship. Recent studies have also reported on how cannabis can reduce some HAART related side effects [62].

These studies highlight the need to identify which intervention may improve adherence among IDUs. When engaged in stable care with an experienced staff and adequate support, IDUs can adhere to HAART and have clinical outcomes equivalent to non-IDU patients [18;63]. Ongoing drug use is therefore not a valid criterion for denying active IDUs access to HAART. Substitution therapy provided with DOT may definitely enhance adherence.

## How to Promote Adherence?

Opiate substitution treatment, such as through the provision of methadone or buprenorphine, is an important tool in promoting HIV treatment adherence among IDUs. However, when OST is available only in specialized clinics, the risk of stigmatization of individuals attending these centers may induce some patients to become reluctant to access or to continue using OST. From another point of view, centers dispensing OST daily may be important entry points for access to HAART for IDUs, as HAART (for instance once a day intake) may potentially be combined with OST, with both being dispensed at the same location and taken under the surveillance of a patient's provider. In this case, only OST interruption may be responsible for poor adherence to HAART.

The advantage of prescribing OST in a different setting, for instance by general practitioners, however, is that stigmatization problems are less present. Under this arrangement, the role of general practitioners (GPs) in OST success and HAART adherence becomes crucial. Creating a link between HAART and OST intakes (e.g. prescribing

a twice a day HAART regimen if OST is also prescribed twice a day) may be beneficial for adherence to both treatments. In countries where GPs do not yet prescribe HAART, GPs should be properly educated about the possible interactions between ART, OST, and other drugs frequently used by IDUs. GPs also should be trained how to properly manage HAART-related side effects and pain; how to create liaisons with HIV specialists and drug treatment centers; and how to better manage or orient the most difficult patients.

While it may be important to start HAART when a patient seems “stabilized” to ensure that he can adhere to treatment, such a delay can have significant repercussions. Delaying HAART can also delay other treatments and have serious health implications for active IDUs who are often affected by other co-morbidities such as hepatitis B, C or tuberculosis.

It is important to remember that OST also plays an essential role in HIV prevention. It has been shown that heroin users on methadone treatment are four to six times less likely to become infected with HIV, either because they stop injecting heroin or are able to have greater control over their heroin use because they are less subject to withdrawal symptoms [55]. Similarly, in a cohort of HIV-infected IDUs on buprenorphine substitution treatment in France [64], among the individuals who remained on OST, a reduction of injecting behaviors was observed over time while buprenorphine injection misuse only pertained to patients who were severe addicts or polydrug users and presented depressive symptoms. Ongoing clinical trials based on buprenorphine substitution treatment to help reduce HIV transmission in China and Thailand (trial HTPN 058) are likely to provide more useful information on OST and HIV prevention.

As more becomes known about achieving adherence through comprehensive treatment regimens, it is increasingly clear that a number of combined approaches will be required to meet the needs of different IDU populations. Two recent reviews [65;66] report the efficacy of different interventions for improving adherence. However, studies which have shown a significant effect of such interventions on virological response are sparse [67].

The use of Directly Observed Therapy (DOT) programs has generated a variety of studies reporting encouraging results. Under DOT, providers observe patients taking their antiretroviral doses daily or less frequently in methadone maintenance treatment clinics [55]. It is worth noting that DOT has been successful even for cocaine users on methadone [68].

When an opiate user is not on maintenance treatment, an efficient role may be played by peers from the community [69] who can perform tasks such as accompanying patients to medical appointments, providing education, and offering adherence assistance that may include DOT, risk reduction, and crisis intervention.

The fundamental element in any of these approaches is that they come as interventions during the initial phase of treatment. Interventions are crucial in this phase because they can establish the patterns that will help patients achieve the 100 percent adherence required for long term virological and immunological success. During the maintenance phase, regular interventions should be planned to avoid extreme episodes of nonadherence, which are detrimental for long term virological response.

## Conclusions

HIV-infected IDUs do not have a faster clinical progression of their disease but a delay in access to HAART, comorbidities and poor adherence, all of which can negatively influence the clinical course of this disease.

In some cases it may be worthwhile to delay HAART initiation in order to address a patient's substance abuse, general stability, or comorbidities that may affect HIV treatment success. However, each treatment strategy (including the treatment sequence for HIV, HCV or other comorbidities and the time of HAART initiation) should be individualized and built into a broader system of medical support, based on the patient's clinical status and readiness to face lifelong adherence and treatment side effects.

However, a patient's active drug use should not necessarily make them ineligible for HAART. A growing body of evidence indicates that more and more drug users are successfully adhering to HAART and achieving full viral suppression. Comprehensive care for these patients should be adequately supplied, and can be achieved by increasing coordination among different care providers; improving patient-provider relationships by overcoming stereotypes about drug use; and supplying adherence support to IDUs starting HAART. Implementing these practices would make a strong contribution toward erasing the differences in clinical outcomes that have marked more vulnerable populations such as IDUs.

## Snapshot: Heroin Maintenance

*Matt Curtis\**

Since its introduction in the 1960s, the treatment of opiate dependency using methadone has proved to be highly successful in addressing the health and social costs of addiction, and reducing HIV infection risk and overall mortality. More recently, buprenorphine has shown great promise as an alternative opiate substitution medication, with results similar to methadone.<sup>1</sup> Buprenorphine has seen widespread use in many countries—notably in France where it is the most commonly prescribed substitution medication—and its use is expanding rapidly in North America.

Not every person has perfect success with methadone or buprenorphine, however: despite these medicines' proven efficacy, a substantial minority of people on substitution therapy continue to use street drugs, especially when receiving inadequate methadone dosing. But recent research points to one possible solution for improving treatment outcomes for people with most severe opiate dependency who have been least responsive to existing therapies.

Since the early 1990s, several research trials have investigated the use of diacetylmorphine—or pharmaceutical heroin—as an opiate substitution medication, largely targeting individuals who have not responded well to methadone treatment. Such programs are generally organized so that patients receive a dose of injectable heroin once or more daily (without take-home doses), which they inject in a supervised setting with sterile equipment provided by the program. Patients are screened at each clinic visit for alcohol or other intoxication to reduce the risk of opiate overdose. In order to achieve a stable daily blood concentration, short-acting heroin is often prescribed in conjunction with a low dose of longer-acting methadone (in either oral or injectable form). Thus heroin maintenance programs have required more infrastructure than methadone or buprenorphine programs, including tighter safeguards on the medication and facilities for supervised injection. Nonetheless, they have been shown to be cost effective, with large estimated savings from reduced health problems and criminality among patients.<sup>2-3</sup>

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The first and best known research trial was conducted in Switzerland between 1994 and 1996. The study involved 1,035 participants with long-term heroin dependence and multiple previous attempts at methadone maintenance or drug-free treatment. An initial attempt to randomize participants into heroin, morphine, and methadone cohorts was not realized, and all participants ultimately received heroin. Though the Swiss research has been criticized for not having control cohorts and other factors,<sup>4</sup> the benefits for participants were promising: treatment retention was higher than for methadone alone; illegal drug use, reported mental health problems, and disease risk behaviors among participants decreased dramatically; and rates of employment and stable housing more than doubled.<sup>5, 6</sup> Although the data on HIV incidence among study participants was not statistically significant, the risk of seroconversion to hepatitis B or C was halved.<sup>7</sup> The number of study participants reporting illegal sources of income fell from nearly 70 percent at baseline to 14 percent at one year.<sup>8</sup> Following the conclusion of the trial, Switzerland passed a referendum to continue heroin prescription as a core component of opiate dependency treatment. More than 2,000 additional people have received prescriptions since 1997.

Soon after the Swiss study results became public, the Netherlands conducted two randomized heroin prescription studies, finding that “supervised co-prescription of heroin is feasible, more effective, and probably as safe as methadone alone in reducing many physical, mental, and social problems of treatment resistant heroin addicts.”<sup>9</sup> In Europe, Germany and Spain have also piloted heroin prescription. Most recently, Canada launched the first heroin prescription trial in North America, the North American Opiate Medications Initiative (NAOMI), which also targets people with longtime opiate dependency and poor outcomes with methadone, and has introduced a third randomized cohort receiving injectable dilaudid rather than heroin. Though results have not yet been published, heroin prescription through NAOMI has proved to be safe, with no deaths or hospitalizations after more than 26,000 injections, and without negative community impact.<sup>10</sup>

The use of prescription heroin maintenance concurrent with antiretroviral therapy has not been documented in case examples or clinical research, although some patients in the Swiss heroin prescription programs have received directly administered antiretroviral treatment as part of the program. Research with heroin prescription in several countries does, however, indicate that it is a safe

and effective tool in addiction treatment, which consequently may be useful in supporting stability and HIV treatment adherence among people with severe opiate addiction who have not responded well to other available pharmacotherapies. The drug interaction profile of prescription heroin is unclear, but it may not require the dosage adjustments necessitated by methadone and buprenorphine interactions with ARVs. Heroin is rapidly metabolized to morphine, which is further converted to morphine-3-glucuronide (which lacks opiate activity) and morphine-6-glucuronide (M6G, which has very potent opiate activity). In contrast to methadone and buprenorphine, it is not currently known whether ARVs affect heroin/morphine metabolism, but heroin is not thought to impede the function of antiretrovirals.<sup>11</sup> Protease inhibitors such as ritonavir and nelfinavir may increase blood concentrations of M6G, but no clinically significant effects have been documented and, as discussed in various chapters in this volume, active heroin users can achieve HIV viral suppression assuming adherence to treatment. For more on possible interactions with ARVs, see the chapter in this volume by Antoniou and Tseng.



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HIV-infected injection drug users are often medically and socially marginalized and outside of traditional systems of care. Directly administered antiretroviral therapy has been suggested not only as a means to initiate therapy, but to provide structure for ongoing adherence.

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# Directly Administered Antiretroviral Therapy for Injection Drug Users

Frederick L. Altice and R. Douglas Bruce\*

## Introduction

The HIV/AIDS pandemic continues to expand globally and injection drug use (IDU) contributes considerably to explosive epidemics in many parts of the world. The WHO 3x5 Initiative, an effort to help those living with HIV by aiming to provide antiretroviral therapy to 3 million people by the end of 2005, has, unfortunately, failed. HIV-infected injection drug users (IDUs), for the most part, have not been considered a central target in the initiative for a number of reasons, including the misperception that they cannot adhere to antiretroviral therapy.

Longitudinal cohort studies conducted during the HAART (highly active antiretroviral therapy) era have demonstrated that adherence to therapy is the key determinant in

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HIV disease progression [1–4]. While adherence remains crucial for all individuals with HIV disease, it may be particularly beneficial for IDUs who have not derived as much benefit from HAART as others. Directly administered antiretroviral therapy (DAART) has been suggested not only as a means to initiate therapy, but to provide structure for ongoing adherence [5].

HIV-infected IDUs are often medically and socially marginalized and outside of traditional systems of care. They also have high rates of psychiatric co-morbidity [6] that can pose problems with adherence to HAART [7]. Active drug use has been linked to nonadherence [8;9] and, despite similar rates of HIV disease progression during the pre-HAART era, progression has been reported to be higher among IDUs than non-IDUs in the HAART era [10–12].

Directly observed therapy (DOT) for the treatment of tuberculosis has been remarkably successful in overcoming obstacles commonly encountered in HIV management by helping to maximize adherence, improve health outcomes, and minimize the development of resistance [13–15]. Yet the non-curative nature of HIV and the complexity of the regimens have called into question the applicability of DOT for the treatment of HIV [16;17]. Recent developments that allow for provision of once-daily HAART regimens, however, are fueling increased interest in DOT for the treatment of HIV in patients with known problems with adherence.

## Underlying Principles of Directly Administered Antiretroviral Therapy (DAART) Programs

Directly observed therapy, unlike the methods used to treat tuberculosis, is not likely to become the method of treatment for all people with HIV. While both HIV and tuberculosis are important global public health issues, cause significant morbidity and mortality if under- or untreated, require at least daily treatment dosing, and result in the development of resistance if adherence is suboptimal, HIV differs in many regards. First, HIV is not transmitted casually and does not invoke the same public health mandate to protect the general public. Second, HIV treatment is lifelong and direct observation may not be sustainable. Third, there is a lack of infrastructure currently available to provide expansive DAART for HIV. Therefore, if DAART programs are going to be effective, they must be user-friendly and provide a value-added service that is perceived to benefit the HIV-infected client.

It is essential to recognize several important issues before implementing a DAART program. First, not all drug users have problems with adherence to HAART. Second, clinicians and other providers poorly predict adherent from non-adherent patients.

Third, an HIV-infected drug user with poor adherence may not require a lifetime of DAART; therefore, such programs should be flexible enough to accept and transition clients to and from the program as needed. Finally, a drug user who is poorly adherent at one point may become more adherent in the future and vice-versa; consequently, frequent assessments of adherence and proactive referral of patients to services are required.

## Models for Directly Administered Antiretroviral Therapy

Many models for providing DAART have been developed and generally fall into two major categories (See Table 1): 1) community-based outreach; and 2) integration into existing structural frameworks. There are advantages and drawbacks to each approach and, in many ways, they are complementary.

### **Community-based Outreach**

Community-based DAART has the benefit of being more flexible, and can engender social support by fostering the development of significant interpersonal relationships between the outreach worker and the patient. Each of these factors has been associated with improved adherence. Much of the model is based on community outreach that has been proven to be highly effective for patients with severe mental illness [18;19] and the homeless [20–23]—both co-morbidities that are highly prevalent among drug users. By nature of its outreach, community-based DAART allows for respect of the patient by engaging the patient on his or her own “turf.” Successful programs have also been conducted in home settings [24] and through mobile outreach programs [25;26]. Limitations to the sustainability of these programs include the magnitude of the effort by outreach workers and the potential cost of the services. Such programs do, however, have the greatest potential for success when working with patients who are active drug users, suffer from cognitive impairment, and generally lead chaotic lives in which the extent of intervention is flexible and can be modified with the changing needs of the individual [27].

### **Integration into Existing Frameworks**

Integration of DAART into existing structural frameworks has been accomplished in methadone clinics [28–30], within buprenorphine maintenance programs [31], prisons [32;33], mobile health clinics [25;26], and residential treatment centers [34]. Opiate maintenance programs, such as methadone or buprenorphine treatment settings, are

an ideal context for individuals who are stabilized on opioid agonist treatment. The limitation of this approach is that very few of the world's HIV-infected drug users have access to effective opioid substitution therapy. Factors that could lead to better outcomes for these patients are the reduction or cessation of active drug use, treatment for comorbid psychiatric conditions, and the degree to which patients are stabilized within the program. While the majority of experience is within methadone maintenance programs (MMPs) where dosing is typically observed on a daily basis until the patient has demonstrated considerable stability, buprenorphine is becoming increasingly available as an effective alternative which also offers the potential to stabilize patients who would otherwise be deemed ineligible for HAART treatment. In some countries, buprenorphine is less regulated than methadone and does not require the rigid structures imposed by methadone treatment programs, thus allowing new opportunities for the possible integration of HIV and drug treatment services into the HIV clinical care setting [31].

Despite the possibilities, integrating HAART treatment into opioid maintenance therapy programs does face a number of challenges. First, there are several pharmacokinetic drug interactions between antiretroviral medications being prescribed and opioid agonist therapy (see chapter eight for a detailed discussion of common drug interactions between opioid substitution therapy and common antiretroviral medications). For example, two of the first-line agents in the WHO 3x5 Initiative include nevirapine and efavirenz, both of which result in marked reductions in methadone levels and subsequent development of symptomatic opiate withdrawal in a significant number of individuals [35–37]. Unless clinicians are aware of this important interaction and willing to increase methadone doses adequately when opiate withdrawal symptoms begin, patients are likely to discontinue HIV treatment, methadone treatment or both [35]. While there are few studies that carefully examine drug interactions between HIV medications and buprenorphine, it does appear that efavirenz results in significant reductions in buprenorphine levels. However, these may not be associated with symptomatic opiate withdrawal due to the lack of metabolism of buprenorphine by cytochrome P450 2B6 isoenzymes and the higher binding affinity of buprenorphine to opioid *mu* receptors compared to methadone [38]. Second, there is the difference in cultures between drug treatment experts and HIV specialists. The drug treatment field, particularly methadone maintenance programs, has been predicated on imposing strict behavioral requirements and punishing anything less than perfect behavior [39]. HIV treatment specialists, on the other hand, have been more advocacy-oriented and typically use rewards rather than punishment. Third, while there have been many effective models of integrating HIV treatment [40;41], and even DAART into methadone maintenance programs [28;30;42], the perception that these treatments cannot be effectively integrated has been difficult to overcome in many settings, particularly

where opiate agonist therapy is tightly regulated. While integration of services has been advocated by many, others have concluded that patients stabilized on methadone can be effectively referred off-site for HIV treatment [43]. Finally, successful treatment typically will require a common commitment to comprehensive care by both HIV providers and drug treatment experts. These providers and experts should be willing to engage in potential cross-training and expertise sharing as well as to work toward integrating services to improve health care delivery for the patient and focusing less on the clinician or clinical site of care.

## Convenience

Convenience factors must be divided into those that are convenient to the patient versus convenient for the health care system. In settings where DAART is required before a patient can receive HAART, it is most likely that the convenience for the patient will be trumped by the convenience for the health care system. In the long run, such an approach is short-sighted but certainly understood when resources are scarce. Fortunately in most settings where HAART is made available, DAART is usually (though not exclusively) considered a value-added service to help those individuals with problematic adherence. Settings in which DAART is available can indicate that patient convenience factors are given the highest priority. In MMPs, patients already come for observed therapy so it is typically not redundant for them to receive an additional array of medications in an observed fashion. In community settings, however, it is important to do a number of things to improve the likelihood of actually using the DAART program. For instance, if in settings where geography creates barriers to access to a DAART program, having multiple sites would likely improve utilization. The expectation that patients will travel many miles by foot, car or bus is untenable and certainly not sustainable. Some programs have anecdotally reported great success with DAART in such settings, particularly where HAART is a scarce resource and is provided to patients with the most advanced illness and ends once these patients feel well enough to return to work. Other programs have used a community outreach approach where trained community health workers who are involved in extended social networks provide social support and observed therapy [44]. Such programs have not, however, been tested among active drug users. Other sites have taken a more comprehensive, patient-oriented approach to DAART for drug users. These sites conducted extensive mapping of the community for drug use and HIV, and assessed the availability of drug services and social support services for people living with HIV. In such settings, the likelihood for sustainability and utilization is greatest [25]. Other efforts, however, have taken a broader, though potentially more costly approach, by providing DAART services through trained

professionals who go to each patient's home to observe their adherence to HAART [45]. This approach often excludes the HIV-infected drug user from decision-making about how their services should be organized. The examples above suggest that the success of a program can be greatly improved if those implementing it have a clear understanding of local feelings about DAART, and strategically consider the community's ability and level of need to utilize such services [25].

## Flexibility of Program

DAART programs that are based upon principles of community outreach lend themselves best to flexibility. DAART programs embedded within MMPs, for example typically remain very rigid because the MMP is rigid by nature. Flexibility, however, can be integrated into such programs by constructing confidential settings to supervise medications, train staff in cultural competence in HIV care, and to either provide a component of outreach and/or allow subjects to have one or two extra dose packs so clients can take their HIV medications even if they are unable to make it to the methadone program. Irrespective of the DAART model employed, it is essential to remember that clients' lives are not organized specifically around the taking of medications and that DAART programs must be flexible, especially when clients identify special needs such as vacations or obligations to travel in advance.

## Confidentiality

Confidentiality is considered critical in the development of a DAART intervention for people living with HIV infection. The main reason to maintain confidentiality within a DAART program is to minimize stigma among a population that is often stigmatized for their drug use and their HIV infection [46]. Within drug treatment settings, factors that are likely to reduce confidentiality include methadone program staff members who dispense HIV medications to clients in front of other methadone patients. Similarly, a methadone program that has separate rooms or lines for those receiving HIV medicines will allow clients to easily sort out who among them is living with HIV. One way to overcome these liabilities is to set up the methadone program so that all clients are observed taking their methadone in a private setting where the nurse has discretion to dispense methadone and any other kind of service within the privacy of the standard treatment setting. Similar sorts of concerns should be considered if

integrating services into any structured setting, such as clinical care settings (where HIV patients are often stigmatized for being more “difficult”), pharmacies or mobile health care programs.

In community DAART programs where clients are met in their home or in other public settings, the array of confidentiality issues is somewhat different. When a DAART outreach worker enters a house, it can often be unclear to them who within the home knows about the client’s HIV status. Home settings are not controlled as easily as other environments, and the constantly changing presence of friends, other family members or guests makes it impossible for the outreach worker to know who can be approached and under what conditions. Neighbors may eventually note an outreach worker’s consistent visits and, depending on how conspicuous the worker’s clothing, accessories, and/or transportation are, realize the client is a person living with HIV/AIDS and further add to their stigmatization. To avoid these kinds of scenarios, community DAART programs must develop well-worked out plans with contingency options, such as outreach workers calling 10 minutes in advance of arrival to see if the client feels the setting is appropriate for a visit or whether they would like to meet somewhere else.

## Full Versus Modified Observed Therapy

Fortunately, most effective antiretroviral regimens for HIV-infected patients who have not been previously exposed to many antiretroviral medications can be administered once a day [47–49]. For patients who have failed multiple prior regimens and/or those with known antiretroviral resistance mutations, therapy is likely to be more frequent. Deciding upon whether DAART will require each dose to be observed or whether the patient will have some doses observed while others are left to the patient to self-administer is usually an issue of availability of resources. The only data from a modified DAART program suggests that adherence is extremely high (>85 percent) for all observed doses, but drops to nearly 50 percent for all unobserved doses [25]. This finding would suggest that all doses should be observed. It is unlikely, however, that patients and health care delivery systems will be able to observe patients take all of their doses all the time. In such cases, innovative approaches such as the use of cues and reminders and/or incorporation of family and/or friends to help the client with adherence can be incorporated to maximize success. Another consideration for active drug users is the acceptance and incorporation of interruptions into the treatment of patients with intermittently chaotic lives. From a clinical trial’s perspective, this approach has been proven to be inferior to continuous treatment, yet it may be a clinical reality for active drug users who pass in and out of health care treatment settings [45].

## Selection and Training of Staff

The responsibility of observing clients taking HIV medications should not be casually given to anyone. In some settings, it is required by law that trained professionals, such as nurses or pharmacists, be the only ones to administer therapy. In order to allow community-trained professionals who are often more willing and able to work with challenging populations, regulations in other settings will permit nurses or pharmacists to be responsible for the packaging of a patient's medications, while an outreach worker can "observe," but not "administer" the medications. This designation is crucial to avoid the mismatch between patient and professional staff and the increased cost of professional salaries that would make DAART too costly for most settings.

While there does not appear to be any special formula that is required for DAART outreach workers, a term that would be best designated as "DAART specialist," a number of factors should be considered. First, if the outreach worker is a former drug user, it is important to provide feedback and support to this individual to avoid triggers that might lead to loss of his/her own recovery. Second, former drug users may not be optimal DAART specialists if they harbor negative attitudes toward drug use itself. This may lead the DAART specialist to pressure the client relentlessly to stop his/her drug use and lead to increased avoidance in meeting the outreach worker out of shame or stigma. Third, active drug users in some settings may not be allowed to work due to employer and human resource constraints. For those individuals who are present or former users, it is important to provide support and oversight as well as rapid and appropriate assistance if their own drug use begins to interfere with their work. For all DAART specialists, it is essential to train them to meet the patient where s/he is presently and provide continuous information, motivation, and behavioral skills to ensure that the patient remain in care, continue to see his or her health care provider, and to adhere to HIV therapeutics and drug treatment goals. Motivational interviewing has been one such way to foster such skills [50;51]. No matter what other skills sets these individuals have, they must understand the community of HIV-infected drug users, be empathetic and non-judgmental, establish a balance in their boundaries and be self-motivated in performing their job. Without such characteristics, it is unlikely that a DAART specialist will be able to promote the type of social support that is believed to be the most effective component of observed therapy programs [52;53].

## Cues and Reminders

Cues and reminders would seem to be useful tools to enhance adherence, particularly for improving unobserved dosing. Yet, in one large randomized controlled trial, partici-

pants using an electronic timing actually had reduced adherence compared to those who did not receive the reminder. These individuals, however, did not include many active drug users. A meta-analysis of all trials using cues and reminders showed a similar negative effect on adherence, but once again, drug users contributed very little to the study populations. Further studies will have to resolve this issue with regard to the type of cue used, acceptability of the reminder by the subject, and the feasibility or sustainability of using methods that potentially rely on costly technology.

## Availability of Spare Dose Packs

It is unreasonable to expect that all patients will make every DAART visit. During the course of therapy it is likely that patients will miss at least one visit due to events such as other scheduled appointments, weather emergencies, personal emergencies, court dates, and/or transportation problems. In such circumstances, a patient should not be penalized by withholding their medication. Many DAART programs address scheduling problems by providing back-up dose packs of three to five doses of medications to tide a patient over during such situations. In order to continue the spirit of DAART, the DAART specialist would expect to be contacted by the client and receive an explanation for the missed visit, counsel the patient to utilize the spare dose packs, provide support and suggestions about how to get to the next DAART visit (i.e., overcoming obstacles), and be firm, but not coercive in encouraging the patient to continue with DAART. A very real concern is that some patients grow fatigued from DAART or even taking HIV medications and use the pretext of having dose packs as a way to avoid meeting the DAART specialist while not taking the medications. In such settings, DAART specialists should encourage the patient to intermittently let them see the spare dose packs and to have the patient provide the empty spare pack. Presentation of the empty spare pack can help the DAART specialist confirm that the client truly utilized the dose pack under agreed upon circumstances and dispense a new one for future use.

## Availability of Ancillary Services

Numerous studies have demonstrated the benefit of ancillary and integrated services for managing HIV [54], drug dependency [55;56] and other complex medical [55;57] and psychiatric [18;55–60] conditions. HIV-infected drug users have many unmet medical and social needs and as a consequence, have increased medical morbidity and mortality

compared to non-drug using patients. For instance, it makes common sense to integrate HIV and drug treatment services, yet this will work only for those who are motivated enough or capable of being retained in drug treatment. Drug users are at increased risk for tuberculosis, and particularly in resource poor settings, integration of tuberculosis services is rational and forward thinking. Routine medical care, however, also makes sense for DAART patients. They have more medical complications, may not have been previously adherent with HIV medications due to adverse side effects, have a demonstrated, high rate of emergency room use, and need prompt attention to overcome such problems. Additionally, drug users have unmet social needs which often interfere with their ability to be retained in health care. In one study of DAART, subjects who utilized two or more of the ancillary services (medical care, drug treatment, and case management services), had a statistically larger reduction in viral load, increase in CD4 lymphocyte count and threefold reduction in emergency room use [61]. Other programs provide an array of other services and report improved outcomes, yet empirical data are forthcoming [62].

## Duration of DAART Services

To date, there have been no data to suggest the most effective duration of DAART services. Noncomparative studies of DAART have been longstanding and were not designed to answer the question of amount of time required for effective therapy. The only randomized controlled trial of DAART to date provided supervised therapy for six months with impressive viral load and CD4 changes. However, the benefits six months after DAART had been discontinued were less impressive, suggesting that some individuals need a longer duration of treatment. A primary problem, is that it is not yet clear which patients will benefit from DAART and for how long DAART services should be provided. What does seem clear is that many patients whose lives are chaotic benefit from the structure, organization, and social support provided by DAART programs.

## Conclusions

Directly administered antiretroviral therapy is just one way to overcome some of the obstacles faced by HIV-positive IDUs. Not all DAART programs are the same. They differ in terms of whether they are based on principles of community outreach versus integration into an existing health care delivery infrastructure, the types of individuals supervising the medication delivery, and how related services are organized and provided. In settings where DAART is compulsory, it will likely limit access to drug users who have been traditionally constrained by issues of confidentiality. Yet it seems clear

that when constraints such as this and others are overcome, DAART can be one of the most effective ways to provide beneficial care to HIV-infected drug users.

**Table 1.** Models of Directly Administered Antiretroviral Therapy

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**Community Outreach**

- ▶ Outreach workers
- ▶ Home-based delivery

**Embedded within Structural Settings**

- ▶ Methadone maintenance programs
  - ▶ Buprenorphine maintenance programs
  - ▶ Pharmacies
  - ▶ HIV-clinics
  - ▶ Directly Observed Therapy programs for tuberculosis treatment
  - ▶ Mobile health care settings
  - ▶ Residential care settings
- 

**Table 2.** Considerations in Developing a Directly Administered Antiretroviral Therapy Program

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- ▶ Coordination with drug treatment and harm reduction programs
  - ▶ Community outreach versus structured treatment setting
  - ▶ Convenience
  - ▶ Flexibility of program
  - ▶ Confidentiality
  - ▶ Full versus Modified Observed Therapy
  - ▶ Selection and training of staff
  - ▶ Cues and reminders
  - ▶ Availability of spare dose packs
  - ▶ Availability of other services
  - ▶ Duration of DAART services
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Prisoners are the community. They come from the community, they return to it. By protecting and caring for HIV-positive prisoners, we are protecting and caring for our communities.<sup>1</sup>

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# Prisons and HIV Treatment

By Ralf Jürgens\*

## Introduction

In many countries, rates of HIV infection among prisoners<sup>†</sup> are high and a growing number of prisoners are in need of HIV-related care, treatment, and support, including antiretroviral therapy (ART). While prisons are often seen as being isolated from society, the issue of how correctional health services deal with HIV-infected prisoners has important implications for the overall care of people living with HIV or AIDS outside prison walls.

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<sup>†</sup>For the purposes of this paper, the term “prisoner” is used broadly to refer to adult and juvenile males and females detained in criminal justice and correctional facilities during the investigation of a crime; while awaiting trial; after conviction and before sentencing; and after sentencing. The term does not formally cover persons detained for reasons relating to immigration or refugee status, and those detained without charge, yet most of the considerations in this paper apply to them as well. The term “prison” is used to refer to all criminal justice and correctional facilities.

This article reviews some of the main issues related to provision of HIV treatment in prison. It shows that providing access to ART for those in need in the prison context is a challenge, but is necessary and feasible. When provided with care and access to medications, prisoners respond well to ART. Data from developed countries show that adherence levels in prisons can be as high or higher than among patients in the community and emphasize the importance of careful planning for the discharge of prisoners back to the community. A major effort needs to be undertaken to ensure that prisoners in developing countries and countries in transition also benefit from current efforts to increase access to ART.

## Two Epidemics—HIV and Incarceration

### Prevalence of HIV in Prisons

Worldwide, rates of HIV-infection in prisoner populations<sup>1</sup> are higher than in the general population:

- ▶ In Western Europe, particularly high HIV-infection rates have been found in prisons in countries from southern Europe such as Portugal and Spain, which report rates of 20 and 14 percent, respectively.<sup>2</sup>
- ▶ In the United States, many prison systems have rates under 1 percent, although a few systems have approached or exceeded 7 percent among men, and 15 percent among women.<sup>3</sup>
- ▶ In Canada, rates between 1 and 11.9 percent have been reported.<sup>4</sup>
- ▶ In the countries of Central and Eastern Europe and the former Soviet Union, HIV prevalence among prisoners is particularly high in Russia and Ukraine, as well as in Lithuania, Latvia, and Estonia.<sup>5</sup> In Russia, by late 2002 the registered number of people living with HIV/AIDS in the penal system exceeded 36,000, representing approximately 20 percent of known HIV cases.<sup>6</sup>
- ▶ In Latin America, prevalence among prisoners in Brazil and Argentina is reported to be particularly high, with studies showing rates between 3 to 20 percent in Brazil and 4 to 10 percent in Argentina. Rates reported from studies in other countries, including Mexico, Honduras, Nicaragua, and Panama are also high.<sup>7</sup>
- ▶ In India, one study found that the rates were highest among female prisoners, at 9.5 percent.<sup>8</sup>
- ▶ In Africa, a study in Zambia found a rate of 27 percent.<sup>9</sup> In South Africa, prison infection rates in 2002 were estimated at 41 percent.<sup>10</sup>

### *Ongoing Transmission of HIV in Prison*

Most of the prisoners living with HIV or AIDS contract their infection outside the institutions before imprisonment. However, studies have shown that injection drug use is prevalent in prisons in many countries, and that imprisonment increases the risk of contracting HIV infection for injection drug users (IDUs) who continue injecting in prison.<sup>11</sup> This is because those who inject drugs in prisons almost always share needles and syringes, which is a very efficient way of transmitting HIV. Because it is more difficult to smuggle needles and syringes into prisons than it is to smuggle drugs into them, needles and syringes are very scarce. Most often, only a handful of needles will circulate among a large population of prisoners who inject drugs. Often 15 to 20 people will inject using the same equipment.<sup>12</sup>

Sexual activity is generally considered to be a less significant risk factor for HIV transmission in prison than sharing of injection equipment. Nevertheless, it does occur and puts prisoners at risk of contracting HIV infection.

The prevalence of these risk behaviors, coupled with the lack of access to prevention measures in many prisons, can result in the frighteningly quick spread of HIV. A number of countries have shown early indications that extensive HIV transmission would occur in prisons. In Thailand, the first epidemic outbreak of HIV in the country likely began among IDUs in the Bangkok prison system in 1988. Six Thai studies found that a history of imprisonment was associated significantly with HIV infection.<sup>13</sup> Prison-based outbreaks of HIV infection have been documented elsewhere.<sup>14</sup> For example in countries such as Scotland,<sup>15</sup> Australia,<sup>16</sup> Russia,<sup>17</sup> and Lithuania.<sup>18</sup>

### **The Epidemic of Incarceration**

Significant increases in the size of prison populations have coincided with the emergence of HIV. In 2003, experts estimated that 8.75 million people were incarcerated worldwide, with more than half of these in the United States, China, and Russia.<sup>19</sup> In many parts of the world, the unprecedented growth of prison populations is due to increased enforcement of drug laws in an effort to limit the supply and use of illegal drugs. In the United States alone, the incarcerated population increased by 239 percent between 1980 and 1995, and drug-related convictions accounted for 30 to 60 percent of this increase.<sup>20</sup>

As a result of the large number of prisoners convicted for drug-related offenses, the demographic and epidemiological characteristics of current incarcerated populations in many countries are significantly different from what they were two decades ago. Consistent with the nature of the crimes for which they are convicted, incarcerated individuals have a high prevalence of drug dependence, mental illness, and infectious diseases, including HIV.<sup>21</sup> In most countries, with the exception of countries with large

heterosexual HIV epidemics, HIV prevalence rates in prison are closely related to the rate of HIV infection among IDUs in the community and the proportion of prisoners convicted for drug-related offences.

Imprisonment is a common event for many IDUs. In a national study in the United States, approximately 80 percent of 25,000 IDUs had been in prison.<sup>22</sup> In a 12-city WHO study of HIV risk behavior among IDUs, between 60 and 90 percent of respondents reported a history of imprisonment since commencing drug injection and most had been imprisoned on multiple occasions.<sup>23</sup> By choosing mass imprisonment as the main response to the use of drugs, countries have created a de facto policy of incarcerating more and more individuals with HIV infection.<sup>24</sup> For example, in 1997, in the United States there were more than 35,000 prisoners with HIV on any given day. In the same year, over 150,000 of those released had HIV-infection. It has been estimated that, in 1997, 20 to 26 percent of all people with HIV (and 29 to 43 percent of all those infected with HCV) in the United States passed through a correctional facility.<sup>25</sup> Over the last few years in Russia around 300,000 prisoners are released annually, many of whom are living with HIV, HCV, and/or tuberculosis.<sup>26</sup> In Ireland, according to a 1997 report, the average annual prison population was around 2,200, with about a turnover of 10,000 prisoners going in and out of the system every year and serving, on average, sentences of 3 to 4 months. Out of the estimated 1,600 people in Ireland with HIV, 300 to 500 had been through the prison system.<sup>27</sup>

Many prisoners serve short sentences and recidivism is common. Consequently, HIV-positive people (and at-risk individuals) move frequently between prisons and their home communities, which they often return to within a few years. The high degree of mobility between prison and community means that communicable diseases and related illnesses transmitted or exacerbated in prison do not remain there. When people living with HIV and HCV (and/or tuberculosis) are released from incarceration, prison health issues become community health issues.

## The Challenge for Prison Health Care Services

Having up to one-fourth of the HIV-positive population pass through prisons represents enormous challenges, but also great opportunities for providing them with care, treatment, and support, including ART. Prisons are key points of contact with millions of individuals living with or at high risk of HIV infection who are largely out of reach of the medical system in the community.<sup>28</sup> In most countries, minority populations, which are overrepresented in the prison population, are the ones that are hardest hit by HIV and tend to have disproportionately less access to health care in the outside community.<sup>29</sup>

For many prisoners, imprisonment thus becomes one of the few opportunities to obtain much needed health care and counseling. According to Bobrik,

[P]roperly organized correctional health services can make a major contribution to society at large by offering medical care and health promotion, by detecting and curing a large number of TB and STI cases, by providing hepatitis B vaccination and HIV counseling, by linking inmates to community services after release, and by assisting in the process of community reintegration. The period of confinement should serve both the health of individual and society at large.<sup>30</sup>

While opportunities exist, the challenges to delivering good care, treatment, and support in prison are great. In many countries, the biggest challenge is the lack of resources, financial and otherwise, devoted to health care in prisons and, more generally, to prison systems. In the few instances where prison care is adequate, the costs of providing it are questioned and efforts to reduce costs lead to deteriorating services.<sup>31</sup>

Compounding the problems are the poor to deplorable living conditions experienced by most of the world's prisoners. Disease is the most common form of death in prisons. International nongovernmental organizations such as Amnesty International, Human Rights Watch, and various regional oversight bodies concerned with human rights systematically investigate and document the living conditions of prisoners, including the abuse of prisoners by prison authorities. Most organizations identify prison overcrowding as a key problem that contributes to stress, poor hygiene, and reduced privacy.<sup>32</sup> Human Rights Watch summarizes worldwide prison conditions as follows:

While conditions of detention vary greatly from country to country and facility to facility, standards in most countries are shockingly low. Prisons and jails in even the richest and most developed countries are plagued by severe overcrowding, decaying physical infrastructure, a lack of medical care, guard abuse and corruption, and prisoner-on-prisoner violence. With the public primarily concerned about keeping prisoners locked up rather than about the conditions in which prisoners were confined, little progress has been made toward remedying these abuses.<sup>33</sup>

Along with fiscal constraints and harsh prison conditions, providing appropriate care to respond to HIV/AIDS among prisoners is often challenged by ideologies and beliefs that prefer punishment to rehabilitation.<sup>34</sup> Additionally, prison health care often has a low status within the correctional system whose priorities and values often conflict with those of medical care. Put simply, "corrections is a public safety or law enforcement activity rather than a public health activity."<sup>35</sup> Harding points out that

[p]rison medicine has a strange identity, stranded in a no man's land between two major social systems, that of health delivery and that of criminal justice. The uncomfortable and marginal status of the discipline is not the result of choices nor orientations of prison health care staff. It is caused by pressures created by criminal justice policy—especially prisons' policy—and decades of neglect by the 'health establishment': ministries of health, medical associations and faculties of medicine have regarded prisons as extra-territorial, as far as health care is concerned. Until the AIDS epidemic, the World Health Organization had not devoted one single activity, consultation or study to the prison environment. Until ten years ago, major medical journals almost never carried articles about health or medical care in prisons. The failures of prison health care have led to serious public health concerns within many prison systems.<sup>36</sup>

## International Human Rights and the Responsibility of Prison Systems

Although prisoners lose their right to liberty, they do retain other rights and privileges except those necessarily removed or restricted by the fact of their incarceration. In particular, states are obligated to provide prisoners with high levels of physical and mental health care comparable to what is available outside the gates of prisons.<sup>37</sup>

The failure to provide prisoners with access to essential HIV prevention measures and to treatment equivalent to services available outside is a violation of prisoners' right to health in international law. Moreover, it is inconsistent with international instruments that deal with the rights of prisoners, prison health services, and HIV/AIDS in prisons, including the UN's Basic Principles for the Treatment of Prisoners,<sup>38</sup> the WHO Guidelines on HIV Infection and AIDS in Prisons,<sup>39</sup> and the UN's International Guidelines on HIV/AIDS and Human Rights.<sup>40</sup>

According to the WHO guidelines, "[a]ll prisoners have the right to receive health care, including preventive measures, equivalent to that available in the community without discrimination, in particular with respect to their legal status or nationality."

The guidelines contain explicit recommendations related to access to care and support of HIV-positive prisoners that cover medical care and psychological counseling; follow up treatment; information on treatment options; receiving care and access to clinical trials in prison that are commensurate to what is available in the community; freedom from being forced to participate in clinical trials; and prisoners receiving post-release care based on their consent.

The International Guidelines on HIV/AIDS and Human Rights identify the following specific action in relation to prisons:

Prison authorities should take all necessary measures, including adequate staffing, effective surveillance and appropriate disciplinary measures, to protect prisoners from rape, sexual violence and coercion. Prison authorities should also provide prisoners (and prison staff, as appropriate), with access to HIV-related prevention information, education, voluntary testing and counselling, means of prevention (condoms, bleach and clean injection equipment), treatment and care and voluntary participation in HIV-related clinical trials, as well as ensure confidentiality, and should prohibit mandatory testing, segregation and denial of access to prison facilities, privileges and release programmes for HIV-positive prisoners. Compassionate early release of prisoners living with AIDS should be considered.<sup>41</sup>

## Effective HIV Treatment in Prison Settings

Access to care and treatment, including ARV therapy and medication to treat opportunistic and other infections, varies widely between developed, high income countries, countries in transition, and developing countries.

In developed, high income countries, the right to enjoyment of the highest attainable standard of physical and mental health, in concert with the principle of equal access to care, dictate that prisoners should have access to a high standard of care, including specialist consultation, diagnostic testing (CD4, viral load, viral resistance) and the full range of ARVs licensed for sale within a particular country.

Combination antiretroviral therapy, and in particular highly active antiretroviral therapy (HAART), is one approach to treatment that has produced positive results in both developed countries and in “difficult” contexts such as developing countries<sup>42</sup> and among “difficult” HIV-infected populations, such as injection drug users.<sup>43</sup> In these contexts and among these groups, combination antiretroviral therapy has proven to be effective in obtaining maximal and durable suppression of HIV viral load, restoration and preservation of immunologic function, improvement of quality of life, and reduction of HIV-related morbidity and mortality.<sup>44</sup> Left untreated, most people infected with HIV will eventually go on to develop HIV-related illnesses and die. If they receive antiretroviral therapy, however, they can live in relatively good health for many years. The following sections provide greater detail on the use of prison-based antiretroviral therapy in developed, transition, and developing countries.

## Treatment in Prisons in Developed Countries

In developed countries, many HIV-positive prisoners receive antiretrovirals. Indeed, many HIV-positive people initiate treatment while incarcerated.<sup>45</sup> As a consequence, AIDS-related deaths in prisons have decreased dramatically. In the United States in 1995, 34 percent of all deaths in state prisons were AIDS-related.<sup>46</sup> A study in the pre-HAART era found that the CD<sub>4</sub> cell counts of untreated prisoners declined more rapidly than did those of untreated persons outside of prison. The study attributed the decline to the stress of incarceration itself.<sup>47</sup> From 1995 to 1999, however, AIDS-related deaths decreased by more than 75 percent in prisons in the United States, thanks to the availability of HAART. In 1999, 242 state prisoners (20 per 100,000 state prisoners) nationwide died from AIDS-related causes, compared with 1010 in 1995.<sup>48</sup> The New York State Department of Corrections reported an AIDS-related death rate of 40.7 deaths per 10,000 prisoners in 1990; in 1998, the rate had decreased to 6.1 deaths per 10,000 prisoners.<sup>49</sup> Similar results have been observed in other countries in which ART is available to prisoners.

Studies undertaken in prisons in the United States and a few other developed countries have shown that, when provided with care and access to medications, prisoners respond well to ART. Springer et al. documented, in a retrospective cohort study among prisoners in the Connecticut prison system, that an increase in CD<sub>4</sub> count and a decrease in virus load occurred during incarceration in prisoners treated with antiretrovirals for more than six months: 59 percent achieved undetectable viral loads at the end of their term of incarceration.<sup>50</sup>

### Adherence

A key aspect to obtaining the greatest benefits from ART is adherence to the prescribed regimen. Although the environment in the prison system creates a number of small and large obstacles to adherence, it also provides some advantages as well.<sup>51</sup>

Most studies have shown that levels of adherence among prisoners are as high as those found among HIV-positive persons enrolled in primary care services linked to municipal hospitals, methadone maintenance programs, or research cohorts of injecting drug users.<sup>52</sup> In one study involving two Spanish prisons, reported adherence levels were even higher than in the community.<sup>53</sup>

This adherence is particularly impressive given the number of institutional barriers that prisoners face. Among the most frequent problems cited by prisoners are the unavailability of medicine and patients not being allowed or able to attend medicine calls because of cell “lock downs” or transfers.<sup>54</sup> In most cases, acceptance and adherence to ART by prisoners were based on different factors. Prisoner acceptance of therapy was associated with trust in physician and trust in HIV medications. Decreased adherence

to treatment by prisoners tended to correlate with the side effects, social isolation, and complexity of the antiretroviral regimen.<sup>55</sup> In one study, social isolation was associated with a twelfold increased risk of non-adherence, and every step up in the complexity of an antiretroviral regimen was associated with a threefold higher risk for non-adherence.<sup>56</sup> In another study, among incarcerated HIV-infected women, both acceptance and adherence appeared to be significantly related to the prisoner's interpersonal relationships with physicians and peers.<sup>57</sup>

### **Modalities of administration of treatment**

The modality of ART administration can profoundly affect adherence to treatment. Some correctional health services administer antiretrovirals under direct observation. The high level of adherence to therapy required to maintain virus suppression (over 95 percent of drug doses taken<sup>58</sup>) may justify directly observed therapy. Alternatives to DOT include modified DOT and “keep on person” (KOP). With modified DOT, patients receive their daily antiretrovirals by swallowing the morning dose in front of the staff and then self-administering later doses. Under KOP, patients keep the full box of drugs with them in their cell (when refrigeration is not necessary) and self-administer ART.<sup>59</sup> Any of these strategies can be chosen, and they are sometimes used simultaneously in the same prison, with different patients. Advantages and disadvantages of each modality have been described extensively by Pontali.<sup>60</sup> Studies to date have provided mixed evidence about which modality is preferable.

An Italian study comparing DOT with modified DOT showed that the DOT group had significantly better virological and immunological results.<sup>61</sup> Fischl et al. also presented data supporting the effectiveness of DOT. They compared the virological responses of HIV-positive prisoners and non-prisoners enrolled in the same AIDS Clinical Trials Group trials who were receiving three or four drug combination regimes. At week 80 of the study, 95 percent of the prisoners who received medication with use of DOT had virus loads of under 400 copies/mL, compared with only 75 percent of the nonincarcerated persons, even though the prisoners had lower CD4 cell counts and higher HIV RNA levels at baseline.<sup>62</sup> However, it is unclear whether DOT accounted for the differences in virologic outcomes in this observational study or whether people in prison have better adherence to drug therapy for other reasons, such as because they are receiving treatment for mental health disorders and their illegal drug use is decreased.<sup>63</sup> In another prison observational study, Wohl et al. showed there was no significant difference in adherence, as measured by electronic memory caps, between self-medication and DOT.<sup>64</sup> Altice et al. also found that the degree of adherence was similar for patients who self-administered their medications (85 percent) and for those receiving DOT (82 percent).<sup>65</sup>

## **Confidentiality**

Waiting in long lines to receive DOT medication may deter some prisoners from starting or continuing therapy. Prisoners may fear being labeled as HIV-positive if they are seen in line for medications several times a day, and thus DOT may result in a break in confidentiality.<sup>66</sup> Altice et al. reported that a significant number of participants in their study reported feeling socially isolated because of being HIV-positive, and many prisoners reported keeping their HIV status hidden from the other prisoners.<sup>67</sup> Wohl et al. found that 68 percent of participants responded that they would prefer to take medication on their own rather than having it provided via DOT. Frequently standing in lines that compromised their confidentiality was a major concern for many of these prisoners.<sup>68</sup>

## **Continuity of care**

Wood et al.,<sup>69</sup> Palepu,<sup>70</sup> and Stephenson et al.<sup>71</sup> all found that the transition between prison and the community is often associated with interruptions in care and treatment, with deleterious effects on virological and immunological outcomes. Springer et al. documented the effectiveness of ART among HIV-positive prisoners, but found that individuals who were reincarcerated had a log increase in viral load and a mean decrease in CD4 lymphocyte count of 80 lymphocytes/ $\mu$ L.<sup>72</sup> Reincarceration may be associated with relapse to drug use, discontinuation of therapy, and, possibly, uncontrolled mental illness. The gains in health status made during the term of incarceration were lost among reincarcerated persons, underscoring the need for linkage to aftercare services for people with HIV infection upon release.<sup>73</sup>

Ex-prisoners face multiple challenges upon release to the community, highlighting the importance of aftercare, particularly in the context of prisoners with a history of drug use. For prisoners living with HIV, these challenges can present significant barriers to continuing medical care. Because prisons are only way stations for most accused persons, careful prison discharge planning is key to preserving the health care advances made in prison, and it requires a comprehensive approach.<sup>74</sup> Effective planning will consider issues such as job placement, treatment of drug use, mental illness triage and referral, appointments for HIV and other medical care, and referral for assistance with housing. Good planning can also help ex-prisoners adhere to their treatment by providing services to assist with social stabilization, transportation, and child care.<sup>75</sup> In Rhode Island, model linkage programs providing good discharge planning that was initiated well before prison release, reduced the rate of recidivism at twelve months among HIV-positive women from 39 percent to 17 percent<sup>76</sup> and reduced the rate of recidivism at two years for a Massachusetts jail cohort from 72 percent to 49 percent.<sup>77</sup> It has been speculated that these results could also apply to HIV care follow-up and regular continuation of ART.<sup>78</sup> Preliminary experiences show that this link between prison and community

is feasible and is essential to obtain continuity of HIV care.<sup>79</sup> In addition, discharge planning and linkage to community aftercare not only maintains continuity of medical care, it also facilitates ongoing secondary prevention efforts.<sup>80</sup>

The importance of continuity of care from prison to community also highlights the significance of maintaining care as a prisoner moves around within the penal justice system. Transfers from one prison to another or court dates may result in problems coordinating medical care and supplying medications in a timely fashion.<sup>81</sup>

### **Comorbid conditions**

Many people living with HIV in prisons also live with HCV, and many HIV-positive prisoners continue to harbor, spread, and acquire tuberculosis.

A number of recent studies have demonstrated that HCV treatment is feasible and promises to be efficacious in correctional populations.<sup>82</sup> [For more information about treatment for HIV and hepatitis coinfection, see chapters five and six]

For prisoners living with HIV, tuberculosis poses a particularly strong health threat. HIV infection is the most important risk factor for the development of tuberculosis and tuberculosis is the main cause of death among people living with HIV. There is also evidence that tuberculosis may increase the speed of replication of HIV. Some reports estimate that tuberculosis is 100 times more common in prisons than in the community. Substandard prison living conditions, including overcrowding, poor ventilation, and inadequate nutrition, exacerbate the attempts to control the spread of tuberculosis in prisons. Moreover, prisons in geographically disparate locations ranging from Thailand to New York State to Russia have reported high levels of drug-resistant tuberculosis relative to the general population.<sup>83</sup> [For more information about treatment for HIV and tuberculosis coinfection, see chapter seven]

## **HIV Treatment for Prisoners in Developing Countries and Countries in Transition: Time to Act**

For countries in transition and developing countries, the international community's commitment to the principle of equivalence of care in the community and in prisons, as well as the willingness of domestic governments to subscribe to the principle, is being tested in the context of the WHO 3X5 campaign.

To date, very little information exists about what is being done to ensure that prison systems are an integral part of scale-up efforts, and there are no published studies or even guidelines on this issue. As recently as December 2005, a news article in the *British Medical Journal* reported that a South African prisoner who was convicted of

murder and who has AIDS had won the right to die at home with his family. The article mentioned that the prisoner had not been treated with antiretrovirals, “although this treatment should be available in the country’s prisons.” The number of deaths among South African prisoners from what are known as “natural causes” has risen steeply, and most of these deaths are caused by AIDS.<sup>84</sup> Despite an earlier court decision granting prisoners access to ART in prisons, it is not known how many prisoners are on ART.<sup>85</sup> South Africa’s Department of Correctional Services is currently reviewing an HIV/AIDS policy for offenders proposal and has indicated that they will include prisoners in the implementation process of ART roll-out in the provinces. The department admitted that it is facing a number of tough challenges, including the increasing prevalence of HIV in prisons, growing complications in the management of TB, making security arrangements for prisoners on ART to receive medication and undergo examinations at community-based treatment roll-out centers, and ensuring access to treatment after release from prison. A commentator noted that the department must be able to provide access to ART “without missing a beat,” because of the negative consequences for both patients and public health if treatment is interrupted or terminated.<sup>86</sup> In March 2006, more than 200 HIV-positive prisoners ended a two-day hunger strike after authorities agreed to address their demands for treatment.<sup>87</sup> In a December 2005 analysis of Zambia, Simooya and Sanjobo noted that “living with HIV/AIDS and indeed many other chronic illnesses in prisons, is still a double sentence for inmates in many parts of the world.”<sup>88</sup> The authors pointed out that few countries adhere to the principle of equivalence of care. In 2004 alone, 449 prisoners died of AIDS-related illnesses in Zambian prisons, and that only a few prisoners living with HIV or AIDS were on ART—despite the fact that Zambia has been relatively successful in scaling up access to treatment in recent years.<sup>89</sup> In conclusion, Simooya and Sanjobo wrote:

Given this background, it is imperative that standard HIV/AIDS services backed by an aggressive campaign to improve living conditions in prisons are urgently needed in Zambia and other countries affected by the AIDS pandemic. These services must be equivalent to those found outside and should include counseling services as well as access to antiretroviral therapies.

All over the world, people with HIV/AIDS are now living longer and more useful lives, and those of them living in prisons must not continue to suffer from an infection whose management is now well understood. There is no legal, medical, or moral justification for HIV/AIDS to continue being a double sentence in prisons.

Some prison systems in Eastern Europe and the former Soviet Union have started small treatment programs, or have started educating prison health-care staff in preparation of such programs. Nevertheless, compared to what is needed, little seems to be happening. For example, Bobrik estimated in 2004 that only 2 to 3 percent of prisoners with HIV or

AIDS (i.e. about 1,000) in the Russian Federation had clinical need of HAART.<sup>90</sup> But in five years, about 70 percent (25,000) would be in need of such treatment. Ensuring a sustainable HIV treatment program that is integrated or at least linked to Russia's general HIV treatment programs and effectively meets the needs of the growing number of prisoners with HIV/AIDS will be a formidable challenge.

## Conclusions and Recommendations

**1. Prisons must ensure that prisoners receive care, support, and treatment equivalent to that available to people living with HIV/AIDS in the community, including uninterrupted HAART.**

The advent of combination antiretroviral therapy has significantly decreased mortality due to HIV infection and AIDS in countries around the world where ART has become accessible. There has been a parallel decrease in the mortality rate among incarcerated individuals in prison systems in those countries. Providing access to ART for those in need in the context of correctional facilities is a challenge, but it is necessary and feasible. Studies have documented that, when provided with care and access to medications, prisoners respond well to antiretroviral treatment. Adherence rates in prisons can be as high as, or higher than, those of patients in the community, but the gains in health status made during the term of incarceration may be lost unless careful discharge planning and linkage to community care are undertaken.

**2. As ART becomes increasingly available in developing countries and countries in transition, it will be critical to ensure that ART is also available in those countries' prisons. Ensuring continuity of care from the community to the prison and back to the community, as well as continuity of care within the prison system, is a fundamental component of successful treatment scale-up efforts. These efforts must take place at the international, national, regional and local levels.**

### *International*

At the international level, access to treatment initiatives by the WHO and other organizations need to include prison-specific components and ensure that prison systems are included in technical assistance missions. These initiatives must also collect and publish data about treatment access and coverage in prisons; highlight, develop, and disseminate models reflecting good and best practices; and bring policymaker and funder

attention to the public health and human rights implications of inadequate treatment access in prisons. In addition, the Global Fund and international donors must be sensitized to the issues related to HIV/AIDS in prisons and funding made available specifically for prison HIV/AIDS initiatives, including initiatives to improve health care services in prisons and the general conditions that impact prisoner health.

#### *National*

Several steps are needed at the national level: (1) prison departments must have a place within the national HIV/AIDS coordinating committees, and prison issues need to be part of the agreed HIV/AIDS action framework and country-level monitoring and evaluation system; (2) prison departments need to be involved in all aspects of treatment scale-up, from applications for funding (to ensure that funds are specifically earmarked for prisons), to development, implementation, and monitoring and evaluation of treatment roll-out plans; (3) the ministry responsible for health and the ministry responsible for the prison system need to collaborate closely, recognizing that prison health is public health; alternatively, governments should assign responsibility for health care in prisons to the same ministries, departments, and agencies that provide health care to people in the community (see below); (4) guidelines should be developed specifying that people with HIV or AIDS are allowed to keep possession of their medication, or are provided with medication, upon arrest, during incarceration, and at any time they are transferred within the system or to court hearings. Police and correctional officers need to be educated about the importance of continuity of treatment.

#### *Regional and Local*

Finally, prisons should form partnerships at the regional and local levels with health clinics, hospitals, universities, and NGOs (including organizations of people living with HIV or AIDS) to provide health care and other services for prisoners, and develop integrated rather than parallel care and treatment programs.

### **3. Make substitution treatment available in prisons and recognize its increasingly important role in facilitating delivery of antiretroviral therapy to IDUs.**

In many countries, a substantial number of people who need ART are IDUs. For them, access to substitution therapy is often a prerequisite for being able to take antiretroviral medications. Maintenance therapy enables opioid dependent drug users to stabilize their lives, and avoid or manage many of the complications of injection drug use, and is an essential component in strategies for retaining active IDUs in treatment.<sup>91</sup> It also provides additional entry points for scaling up ART, improves drug adherence, and increases access to care.<sup>92</sup> Where substitution therapy is available in the community, it therefore

also needs to be available in prisons, so that people on substitution therapy and ART are able to access both without interruption.

**4. To increase access to care and treatment, including ART, prison systems should increase access to HIV testing. In particular:**

- ▶ offer prisoners HIV testing upon entry and routinely throughout their imprisonment so they can exercise their right to know their HIV status; and so that those who do test positive for HIV can benefit from access to care, treatment (including ART), and support.
- ▶ provide HIV testing always on a voluntary basis with anyone who is tested giving informed consent and having access to pre-and post-test counseling.
- ▶ link HIV testing and counseling closely to access to care, treatment, and support for those testing positive. Testing and counseling should also be part of a comprehensive HIV/AIDS program that includes access to prevention measures.

There is evidence that programs that routinely offer HIV testing on entry to prison result in a large number of prisoners accepting HIV testing,<sup>93</sup> particularly if HIV testing is part of a comprehensive care and treatment program for HIV-positive prisoners and if HIV test results are kept confidential and those who do voluntarily disclose their HIV-positive status do not face discrimination or abuse.<sup>94</sup> In contrast, policies of mandatory testing and segregation are counterproductive.<sup>95</sup> HIV is not transmissible via casual contact (as is active TB, for example), and therefore mandatory testing and segregation of people living with HIV in prisons is not necessary for public health purposes. In addition, mandatory testing and segregation can have negative health consequences for segregated prisoners. In the United States, segregating HIV-positive inmates at a South Carolina prison contributed to a tuberculosis outbreak in which 71 percent of prisoners residing in the same housing area either had new tuberculosis skin-test conversion or developed tuberculosis disease. Thirty-one prisoners, and one medical student in the community's hospital, subsequently developed active tuberculosis.<sup>96</sup>

**5. Prison health care needs to be appropriately funded and evolve from its current “sick call” model into a proactive system.**

As early as 1992, a joint position paper by the American College of Physicians, the National Commission on Correctional Health Care, and the American Correctional Health Services Association, spoke of a “crisis in correctional health care.” The paper pointed out how incarceration of large numbers of drug users, many of them living with HIV or AIDS, has exacerbated existing problems in health care provision in prisons.

It recommended, among other things, that correctional health care budgets reflect the growing needs of the prison population; that correctional health care be recognized as an integral part of the public health sector; and that correctional care evolve from its present reactive “sick call” model into a proactive system that emphasizes early disease detection and treatment, health promotion, and disease prevention.<sup>97</sup> These recommendations are consistent with those of a more recent study of health care services in federal prisons in Canada. The study acknowledged that there is a need for a public health infrastructure to fulfill the core functions of public health services within prisons by implementing measures to assess, protect, and promote prisoners’ health status; effectively surveying for infectious and chronic diseases; coordinating actions to prevent diseases and injuries; and evaluating the effectiveness, accessibility, and quality of health services. The study concluded that “addressing [prisoners’] health needs will contribute to the inmate’s rehabilitation and successful reintegration into the community.”<sup>98</sup>

## **6. Strongly consider the positive impact that transferring control of prison health to public health authorities can have on HIV/AIDS care in prison.**

In the vast majority of prison systems in the world, health care is provided by the same ministry or department responsible for prison administration, not by the ministry or department responsible for health care. Prisons were not designed and are generally not equipped to deal with prisoners infected with chronic, potentially fatal diseases such as HIV/AIDS, hepatitis, and tuberculosis. They do not have adequate staffing levels, adequate staff training or adequate equipment to meet the health needs of prisoners suffering from these diseases. The authority and influence of prison officials may compromise the ethical obligations of health care professional. In instances where prison health care staff are committed to fulfilling their ethical duty to prisoners and to providing adequate health care, prison administration and security staff often impede them from doing so. Trust and confidence are crucial to an effective, ethical relationship between patient and health care provider. When health services for prisoners are subservient to the prison administration it is unlikely that prisoners will trust or have confidence in the health care providers. This lack of trust contributes to substandard health care for prisoners.<sup>99</sup>

Experience in a variety of prison systems has shown that health care in prisons can be delivered more effectively by public health authorities than by prison management. This has the advantage of strengthening the link between health in the community and health in prisons.<sup>100</sup> Norway was one of the first countries to initiate such a change in prison health administration, and France has had good results from its 1994 transfer of prison health management to the Ministry of Health and its pairing of every prison with a public hospital.<sup>101</sup>

**7. As prison systems develop and implement treatment and care programs, special attention should be given to information and services designed to meet the needs of women prisoners.**

Since there are fewer women than men in prison, the health services provided for women are sometimes minimal or second-rate. With the advent of HIV/AIDS, a new problem has arisen for women prisoners. Women prisoners need the same preventive measures and the same level of care, treatment, and support as male prisoners. However, there is an additional need for initiatives that acknowledge that the problems encountered by women in the correctional environment often reflect, and are augmented by, their vulnerability and the abuse many of them have suffered outside prison. The task of protecting women prisoners from HIV transmission and of providing those living with HIV or AIDS with care, treatment, and support, presents different—and sometimes greater—challenges than that of dealing with HIV infection in male prisoners.

**8. Ultimately, priority must be given to reducing the number of people who are in prison.**

Imprisonment cannot be seen as providing a short or longer-term solution to individuals' and societies' problems with drugs. Studies have shown that fear of arrest and sanctions is not a major factor in an individual's decision about whether to use or deal drugs. There is research that also shows little correlation between incarceration rates and drug use prevalence in particular countries or cities; and that the impact of enforcement action on price is much less powerful than other market factors.<sup>102</sup> Given the significant costs of incarceration as a way of reducing drug problems, it is hard to justify a drug policy approach that prioritizes widespread arrest and harsh penalties for drug users on grounds of effectiveness. Many of the problems created by HIV infection and by drug use in prisons could be reduced if alternatives to imprisonment, particularly in the context of drug-related crimes, were developed and made available. As early as 1987, WHO, in a statement from the first Consultation on Prevention and Control of AIDS in Prisons, noted that “[g]overnments may...wish to review their penal admission policies, particularly where drug abusers are concerned, in the light of the AIDS epidemic and its impact on prisons.”<sup>103</sup> The fact that many governments overlook this suggestion continues to drive an ever growing public health and criminal justice crisis.



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More than 1,000 patients have been receiving ART in 13 health institutions for up to 8 months, with about 15 percent of them in prisons. During this period, treatment retention has been approximately 95 percent.

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# The GLOBUS Project: First steps to Antiretroviral Therapy for Injection Drug Users in Russia

Alexei Bobrik, Valeria Letyagina, Natalia Vasilieva\*

## Introduction

The first case of HIV infection in Russia was diagnosed in 1985, but the epidemiological situation started to significantly deteriorate in 1996, when a number of Russian regions reported serious HIV outbreaks among injection drugs users. Between 1996 and 2001, the number of new HIV cases grew rapidly, after which the registration of new infections slowed. The infection rates' rise and fall has been interpreted very differently by various analysts. Some question the decrease in incidence, noting weak surveillance systems and a significant decline in state-sponsored HIV testing concurrent with the change in reported incidence [1]. Others claim that the Russian HIV epidemic has stabilized and is developing according to a relatively optimistic scenario [2;3]. Another group views declin-

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ing incidence as temporary, attributed mainly to the epidemic's transition to a second phase characterized by transmission of HIV from primarily injection drug users (IDUs) to the general population [4]. By May 2006, the total number of officially registered cases of HIV in Russia exceeded 350,000 [5], but the actual number of infections seems to be much higher. According to UNAIDS data, a median estimate of 860,000 people are currently living with HIV/AIDS in Russia, with low and high estimates ranging from 420,000 people to 1.4 million [6;7].

Estimates of the number of HIV-related deaths in Russia during the last 10 years vary from 1,200 [2] to over 6,000 [5]. When interpreting these mortality data we should take into account that HIV infection started to rapidly spread in Russia only in the second half of the 1990s, and therefore the great majority of people living with HIV/AIDS (PLWHA) have not yet progressed to AIDS. Accordingly, the full picture of demographic losses and other consequences of HIV/AIDS for the country are not yet clear.

Estimates of the number of people in Russia in need of antiretroviral treatment (ART) vary as well. According to official data not more than 20,000 PLWHA had indications for HAART by May 2006 [2]. A number of national and international experts, however, believe that currently more than 50,000 Russians are in need of ART. As of May 2006, approximately 5,000 patients receive such treatment, meaning only about as 10 percent of the PLWHA needing therapy have access to it in Russia [5].

Institutionally, Russia's response to HIV/AIDS remains shaped by the legacy of the Soviet health system, which was characterized by a range of highly specialized vertical programs with very little horizontal integration even between closely-related subfields. The registration of the first cases of HIV in the Soviet Union in the 1980s led to the creation of a separate, centralized system of AIDS centers that bear sole responsibility for HIV testing and health care for PLWHA.

As a result of these decisions, HIV prevention and treatment was not integrated into primary health care, which undermined the system's ability to provide these services to the public and left health care providers untrained and uninformed about the disease. For many years, these centers suffered from universal underfunding, with the problem compounded by a policy that inappropriately allocated scarce resources for mass HIV screening of the population rather than for targeted surveillance of risk groups or on education, prevention, and treatment. Russia's systematic HIV testing of large population groups misses infections in the smaller high risk groups where they are most likely to occur. Furthermore, the system reports the names of those who test positive to a central registry, which likely inhibits voluntary counseling and testing because of the high level of homophobia, prejudice against drug users, general stigmatization of PLWHA, and limited availability of HIV treatments in Russia. These are the main reasons that official data on HIV incidence and prevalence, as well as the need for ART are widely considered to be understated by a significant factor [1].

## The GLOBUS Project

At the end of 2004, with the financial support of the Global Fund to Fight HIV/AIDS, Tuberculosis and Malaria, an NGO consortium began an HIV/AIDS control program in Russia under the name GLOBUS. The overall goals of GLOBUS are to stimulate an effective national response to HIV/AIDS in the Russian Federation and to spearhead such a response in selected regions. GLOBUS pursues these goals by engaging in HIV prevention activities for the general population, youth, and vulnerable groups; providing treatment and care to PLWHA; and conducting advocacy to promote a more effective fight against the epidemic. Although, the major focus of the project is on HIV prevention, there is a significant treatment component, which is jointly implemented by the Open Health Institute (OHI) and AIDS Foundation East–West.

The major initial challenges of the HIV treatment component of GLOBUS were the high cost of antiretroviral (ARV) drugs registered in Russia, absence of national ART protocols, significant heterogeneity in clinical practice between different regions, and a traditional underestimation and under use of health personnel other than physicians. Taking into account the emphasis of GLOBUS on vulnerable populations, program implementers also recognized a crucial problem in the generally poor ability of government AIDS centers to reach IDUs or to routinely address their multiple complex needs such as overlapping comorbidities, social problems, and increased difficulties with adherence to medications. Moreover, specific clinical challenges for HIV/AIDS treatment in Russia include significant prevalence of hepatitis B and C, and tuberculosis co-infections.

Based on a comprehensive needs assessment in the 10 Russian regions covered by the program [8], the GLOBUS HIV treatment component aims to improve overall access to ART; to create conditions for sustainable HIV treatment programs; and to develop and implement a realistic model of ART for IDUs in Russia.

The first several months of the program were devoted to development of a proper supply chain and negotiations with the pharmaceutical companies to reduce ARV drug prices. Special software was developed to ensure strict individualized ARV drug inventory management. In the absence of national legislation, OHI also had to elaborate all the major documents, including treatment guidelines, and defining the GLOBUS framework of principles for HIV treatment. Taking into account the significant proportion of patients with a history of drug use, a special adherence promotion program was developed based on the experience of the Jumpstart project at Columbia Medical Center in New York City. To ensure the use of a similar approach based on accepted standards, a series of trainings was conducted with the involvement of international technical consultants for the health workers from all GLOBUS regions.

Following the development of documents and trainings, GLOBUS organized the delivery of ARV drugs and laboratory equipment to participating regions and the first

patients were started on HAART. Within several weeks after the initiation of the treatment program, international and Russian technical advisors visited all the regions to assist the treatment teams with this crucial stage of the project. Continuous technical support was provided via telephone and e-mail consultations and repeated visits of OHI experts to the regions.

## ART Program Design

Treatment in all GLOBUS regions is provided at government institutions certified according to Russian legislation. In most cases, these institutions are AIDS centers, or in some cities, infectious disease hospitals. All clinical services within the framework of GLOBUS are provided free of charge. Currently, about 80 percent of the program's patients have a history of injecting drugs, including polydrug use (usually home-made opioids, heroin, vint—a form of injectable methamphetamine—and alcohol). Most of these patients have participated in some form of addiction treatment program in the past.

Despite their past addiction treatment program participation, the majority of patients are unaware of antiretroviral drugs and treatment. GLOBUS program sites have treatment teams to deal with these issues and other patient concerns, consisting of a clinician, a nurse, a social worker, and, at most sites, a trained peer educator. At all sites, AIDS center specialists are strongly encouraged to work closely with local infectious disease hospitals and TB clinics. Local harm reduction projects are actively involved in the program and provide patient recruitment from IDU populations, active social follow up, and referral.

Upon acceptance to the program, all the patients receive intensive education on HIV and the basics of HAART. For potentially problematic clients special efforts are made to adapt the complexity of interventions to the individual's ability to utilize treatment and care. For example, if the start of ART can be postponed, an active injecting drug user can at first be referred to harm reduction services and/or drug treatment.

Another common first step in the program is for patients to undergo evaluation and treatment of comorbid conditions (e.g. STI, TB) and prophylaxis of opportunistic infections to prepare them to cope with more complex ART regimens. Regular visits to the AIDS center also help the patient to adapt behavior conducive to long-term treatment. GLOBUS indications for ART are based on the WHO protocols for the CIS [9]. Generally, the preference is made toward simplified ART regimens that require taking medications twice a day [10].

All patients receive additional counseling and peer support after the start of ART. Patients receive small personal booklets with a list of scheduled events, including sched-

uled appointments and times to take medications. There are currently plans to distribute medications in segmented weekly pillboxes and focused medication adherence counseling. At the initial stage of treatment, medical staff prepare an individualized schedule of clinic visits for each patient, assess adverse side effects, and encourage adherence. Gradually patients reduce visits to the AIDS center to a monthly basis in order to collect medications, and receive clinical and laboratory follow-up. If a patient misses an appointment, an outreach worker from the local harm reduction site will make an inquiry. When patients show indications for decreased treatment adherence, additional counseling is administered, and, if judged necessary, the patient can be directed again to the AIDS center for more frequent visits.

In all GLOBUS regions, treatment is also provided in prisons on a pilot basis. The approach used there is much the same with respect to preparing the patients, counseling, clinical care, and follow-up with the only exception that ARV medications are dispensed under direct observation of prison medical personnel.

## Lessons Learned

As of 2006, three rounds of ARV procurement (totaling 2,000 nine-month treatment regimens) have been successfully completed in the 10 GLOBUS regions. More than 1,000 patients have been receiving ART in 13 health institutions for up to 8 months, with about 15 percent of them in prisons. During this period, treatment retention has been approximately 95 percent. The duration of the treatment program to date is too short to draw firm conclusions about progress, and it is not yet clear which components of the project have contributed the most to its success. However, some initial lessons have been learned.

The high prevalence of comorbid medical conditions among patients suggests the need for ancillary services, including drug treatment, case management, and medical services that are not routinely available in AIDS centers. Unfortunately the existing referral system does not adequately address this issue.

The lack of antiretrovirals in most Russian cities has kept PLWHA and caregivers waiting for HAART for several years, and ART is often perceived as a last-minute lifesaving intervention. It is not yet considered by physicians and patients as an intervention that could be planned jointly and well in advance. As a consequence, initiation of treatment is often associated with concern and irrational fears. In St. Petersburg, for example, there is even a tendency to hospitalize patients for the first two weeks of treatment “to assess tolerance of and adherence to ART.” The conclusion drawn from GLOBUS is that the initiation of treatment should be “demystified” in the eyes of both

patients and doctors, and the period preceding treatment initiation should be used to build mutual confidence and to plan appropriate follow up.

The current vertical organization of AIDS centers seriously limits the possibility of providing ART to people who do not live near these institutions. Special efforts should be made to gradually expand HIV treatment and care practices into the general health care system.

Finally, the legal restrictions on the use of opiate substitution therapies are a serious obstacle to expansion of ART in Russia. Access to these treatments remains severely limited and tightly controlled despite the fact that substitution therapy has been shown to reduce the use of illegal opioids, help normalize the lives of opiate dependent people, and support retention and medication adherence within HIV treatment programs. Considering the large proportion of IDUs among those who need ART in Russia, it is critical that projects like GLOBUS are replicated and expanded on a national level and given the opportunities to use all proven and effective drug treatment options available.

## **Snapshot: Cocktails and Therapy**

*Shona Schonning and Alexandra Volgina\**

Ira found out about her HIV status in 2000. She was also diagnosed with both Hepatitis B and C. She wasn't surprised by the diagnosis but it weighed on her nonetheless. She did not receive any post-test counseling and wasn't even aware that any kind of treatment existed, although at the time antiretroviral (ARV) therapy was available in her city. She had a nine-year old daughter and, aware of the stigma connected with HIV, feared that if anyone found out about her status, her daughter could be kicked out of school. She intentionally avoided seeking medical care. She was distraught and couldn't get her hands on any heroin at the time so she started drinking heavily.

Four years later, Ira was admitted to the hospital with a CD4 count of 23. After two weeks of unstoppable bleeding, Ira and her doctors had little hope that she would survive. But the bleeding did stop, and she began ARV therapy. By 2006, Ira had been receiving ARV therapy for two years. Her last CD4 count was 170 and her viral load was undetectable.

During her two years of adhering to her HIV treatment regimen, Ira has experienced phases of alcohol and drug use and medical issues that challenged her adherence and changed her support needs.

Ira's success has required a carefully designed, client-centered approach. The support Ira has received and the control she has had over her treatment have prompted her to work as a peer counselor for HIV-positive patients in the very hospital where her own healing began. She helps these patients start and stay on ARV therapy using her own experience to provide the same kind of client-centered support that turned her life around.

### **Starting Treatment**

When Ira was admitted to the hospital, she didn't expect or even want to survive. Then one day volunteers from a local NGO led by HIV-positive people visited Ira in the hospital and a new chapter in her life began. The NGO founder, Natalia, was a patient in the same hospital. Natalia told Ira about living with HIV,

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though she had serious doubts about Ira's chance of surviving after seeing her CD4 results. She tried to convince Ira to see specialists at an AIDS center, but Ira resisted. One of the greatest barriers to ARV therapy throughout Russia and the former Soviet Union is that those most in need, many of whom are IDUs, do not come forward for treatment.

"For years, doctors said we were worthless," Ira said. "Now they have decided to treat us. But very few are going to come running to the clinics. People don't trust doctors because of the past—that's what's keeping them away."

Natalia told Ira that she knew a good doctor in the AIDS center who would help her, and Ira sought him out when she was released from the hospital. Yet Ira found that as a drug user and alcoholic she wasn't treated with respect. During one of her visits, a committee of health professionals discussed her fate, ready to condemn her to death as she stood in front of them.

"They spoke about me as if I was some kind of object," said Ira. "They said my alcohol and drug use made me not worth treating. They talked about me as if I wasn't there. I wanted to leave and never come back."

Ira's peer counselors, however, refused to give up on her. They helped her fight successfully for her right to get the medicines she needed. Ira finally felt like someone was taking her seriously, and she started ARV therapy.

Ira now uses her experience to help her patients begin therapy. "The volunteers gave me the strength to get through that hell," she said. According to Ira, the key is to make people feel cared for.

Beside the insensitivity of some doctors, Ira also had to contend with serious side effects when she started therapy. Natalia reassured Ira that the side effects would pass. And she held out. As a counselor, Ira is careful about how she talks to her patients about side effects: "As a rule I don't talk about side effects during the first session," she said. "But they do eventually need to know." Though she doesn't discuss side effects immediately, Ira does let her patients know what to expect. And, like Natalia, she offers them reassurances that the side effects will pass.

"My first priority," Ira said, "is to prevent people from feeling that they have come to yet another clinic where they will be just another statistic." She lets them know right away that she takes them seriously and that they will be the

ones making the decisions. “I let the patients know that they don’t have to start therapy right away,” she said. “I tell them that they have time to gather information, think, and decide for themselves before they start therapy; that it’s their decision—not the doctor’s or anyone else’s.” Once she has established contact with a patient, Ira gives them a tour of the clinic. In addition to telling them what their rights are, she tries to make patients feel comfortable by guiding them through the system, telling them what to expect, and giving them information so that they can make decisions for themselves.

### **Choosing a regimen and staying adherent**

When the AIDS center prescribed ARV therapy for Ira, they did not counsel her about adherence. “The only thing the doctors told me,” Ira said, “was ‘take the white ones with the brown ones—8 AM and 8 PM, and the yellow ones at night 1 AM’...I didn’t even know that it was life-long treatment.” Ira stuck to her regimen, even though it was difficult and she had to take the drugs at very inconvenient times. After a year, Ira found a schedule that worked for her lifestyle and her regimen became easier. Ira’s experience has helped her work with her patients to devise drug taking schedules that cater to their lifestyles and are conducive to adherence. The bottom line for Ira is to give patients control at the outset, because a strong sense of control can improve adherence.

Most of Ira’s patients face a wide variety of serious psychological and social problems. Some are homeless. Most have problems with alcohol or drug use. Ira assesses their needs and helps them find the appropriate services. For some people, one of the first steps to adherence is acquiring basic identification documents, which are required for accessing any kind of medical or social services in Russia. Ira’s cell phone serves as an informal hotline that her patients can use to get help and answers to their questions.

### **Drinking, Drugs, and ARVs**

During the first six months of ARV therapy, Ira did not drink much or use heroin. Some time after her half year of therapy, Ira started drinking heavily, averaging about a liter of vodka a day. The peer counselors found that they had to remind her about her ARV doses more often. Ira’s drinking pattern, however, was well established. She drank on a daily basis in similar settings and quantities. She continued to work and her social situation was relatively stable. She had a systematic way of staying adherent by taking her ARV medications before she got drunk.

Through her own experience and work with her patients, Ira understands how alcohol can undermine adherence. Many of Ira's patients are alcoholics and she has noticed that patients with relatively stable drinking patterns are more adherent than those who engage in binge drinking. Binge drinkers often forget to take their doses, sleep through their dose time, and/or forget to carry their pills with them. They often cannot remember whether they have taken their pills or not. Ira responded to her binge drinker patients by following up with them about their schedules more frequently, encouraging them to drink less, and asking family and friends to more intently remind them to take their pills.

Although Ira's stable drinking did not threaten her adherence, it created other health problems that did. She had frequent flare-ups of pancreatitis and hepatitis-related problems, which often made her so sick that she could not keep the pills down. At times, doctors thought that they would have to take her off of ARV therapy. Ira also experienced severe pain due to an arthritic condition that was not adequately treated. She felt so bad that she didn't want to live and for three days she refused to take her medication. Natalia worked hard to convince her that the pain would pass, and her demonstration of caring made Ira want to live. She began to take her meds again.

Yet Ira continued to suffer. Heroin soon became a tempting cure for pain. As an experienced injecting drug user (IDU), Ira knew how to use heroin and where to find it. Soon her dose and frequency of use returned to the levels they had been before she quit. Despite her renewed heroin use, Ira remained adherent, but social factors began to make her life difficult. She started to have problems with work and she was spending more and more time trying to find heroin.

In many ways, Ira was experiencing the same kinds of challenges that face her patients who use drugs. Drug users' problems with adherence differ from those of alcoholics and are often related to social issues. Alcohol consumption and drinkers are socially acceptable in Russia, whereas drug use is highly stigmatized. Drug users, often scapegoated for many of society's problems, face stigma and discrimination from the general population, medical professionals, and sometimes their own families. Ira, as a peer, helps restore and develop patients' trust in themselves and the doctors in the hospital and the AIDS center. But even though trust is vital, it is not sufficient to keep a patient adherent.

Although IDUs require support similar to that required by alcoholics, Ira feels that drug users, in some ways, are easier to work with than alcoholics. “If you are an IDU, you are already taking drugs all the time,” said Ira. “You are very adherent—why not take ARVs?” The effects of alcohol add to the problem. “When you drink,” she continued. “You can forget the previous evening entirely. You’ll never forget you were taking heroin...IDUs are more stable; are more together in their minds.”

The greater stigmatization of drug users compared to attitudes toward alcoholics, creates a somewhat different set of challenges for IDUs. There are far more services available to alcoholics. Alcoholics are unlikely to be refused medical care whereas it is common for drug users to be refused medical services even in trauma centers. People do not break the law when acquiring alcohol, while drug users face the constant risk of arrest. As Ira noted, “It’s hard to control your life when you are breaking the law several times a day.” Acquiring drugs can be quite time consuming. This, combined with the stigma related to drug use and the effects of drugs themselves, sometimes makes it difficult for drug users to keep their jobs. Unemployment can further destabilize a drug user’s life and have a negative effect on adherence. Since substitution therapy, which stabilizes the lives of IDUs and enables them to have good adherence, is still illegal in Russia, drug users need particularly intense social support to achieve successful adherence.

Although she remained adherent to her ARV therapy while using heroin, Ira’s drug use was creating overwhelming problems at work. After several unsuccessful attempts to quit on her own, Ira received help from her colleagues and went to a rehabilitation center. Ira enrolled in one of the few centers in Russia that utilize evidence-based approaches to treating heroin addiction and handling patients with HIV. Ira’s colleagues at the hospital miss her very much, but expect her to complete her rehabilitation and are keeping her job open for her return.

As a patient, Ira highlights both the complexity and feasibility of successfully administering ARV therapy to a person who uses drugs and alcohol. As a peer counselor, Ira exemplifies the importance and value of developing ARV therapy efforts that directly involve drug users and people living with HIV.



## 2. Major Coinfections



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It seems certain that the presence of HIV infection has a negative impact on HCV related disease progression, and can increase liver-related morbidity and mortality from conditions such as cirrhosis and liver cancer. This is of particular concern for areas of the world where the HIV epidemic is fuelled by the recent increases in injecting drug use.

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# The Natural History of HIV and Hepatitis C Coinfection

Gail V. Matthews and Gregory J. Dore\*

## Introduction

There is now widespread recognition that infection with hepatitis C virus (HCV) will contribute significantly to continuing morbidity and mortality within the HIV-infected population over the coming years. Information on the current prevalence of HCV among people with HIV, as well as on the incidence of newly acquired infections, allows for estimations of the projected burden of disease. Similarly, natural history studies examining the effect of HIV on HCV outcomes and vice versa will enable greater understanding of the reciprocal interactions between these viruses [see Appendix 1 for a summary of HIV's impact on HCV]. This is particularly important as the treatment of both infections continues to evolve and develop. Finally, predictions of the expected contribution

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of liver disease to HIV-related morbidity and mortality allow more accurate allocation of future health resources and services, both in the developed world where treatment for both infections is widely available and in the developing world where access to treatment for HIV is increasing yet anti-HCV treatment remains uncommon.

## Global Prevalence of HIV/HCV Coinfection

Overlapping routes of transmission for HIV and HCV result in a significant proportion of individuals infected with both viruses. However, the prevalence of coinfection in any population varies markedly depending on geographical area, risk factors for HIV acquisition, and whether the prevalence quoted considers that of HIV in HCV-positive persons or HCV in HIV-positive persons. Differences in the ease of virus acquisition through blood borne transmission mean that whilst the rate of HIV infection is low in most HCV-infected populations (usually between 1 and 10 percent) [1;2] the rate of HCV infection in HIV-infected populations is often high (15–50 percent), particularly in settings where a large proportion of HIV cases are acquired through injecting drug use (IDU). Geographical differences in HIV/HCV coinfection prevalence therefore often simply represent differences in HIV risk factors within a population. In a retrospective analysis of an international antiretroviral therapy study (CAESAR) HIV/HCV coinfection prevalence varied from 2 percent in South Africa to 49 percent in Italy [3]. Marked geographical differences in HIV/HCV coinfection prevalence have also been reported within Europe [4–6] and the United States [7;8]. An analysis involving the EuroSIDA cohort of over 3000 patients showed an overall HIV/HCV coinfection of 33 percent [9], but in some areas of southern Europe rates were as high as 50–60 percent, whereas rates of 10–37 percent were seen in northern Europe. These differences are primarily related to a higher proportion of IDU-acquired HIV infection in southern Europe. Similarly, the United States has a significant burden of coinfection with an estimated 240,000–300,000 HIV/HCV coinfecting individuals (a prevalence of 30 percent) [10] but prevalence varies considerably between studies from different states [8]. A cross-sectional analysis of a sample of 1,687 HIV-infected patients from the U.S. ACTG clinical trials estimated an overall HCV prevalence of 16 percent [7], but demonstrated great variability depending on the presence of defined risk factors (self-identified IDUs and haemophiliacs). Seventy-three percent of “high-risk” patients were found to be coinfecting compared to only 4 percent of “low-risk” patients.

## Prevalence of HIV/HCV Coinfection among IDU Populations

Globally, injecting drug use (IDU) remains one of two principal risk factors for HCV infection (the other being unsafe injections in health care settings), and a major risk factor for HIV infection. Duration of injecting, frequency of use, and other injecting behavior have been linked to transmission risk for both HIV and HCV; however, HCV is more efficiently transmitted via IDU than HIV. Harm reduction strategies such as needle and syringe exchange programs (NSPs) have a relatively greater impact on HIV than HCV prevention. In countries with early and widespread introduction of NSPs, HIV prevalence may be very low among IDU populations despite high HCV prevalence. For example, HIV and HCV prevalence among regular injecting drug users (IDUs) in Australia is 1 percent and 50–60 percent, respectively [1]. Thus, HIV/HCV coinfection is relatively uncommon in Australia. In contrast, countries such as the United States, where harm reduction coverage has been more limited, have considerably greater rates of HIV/HCV coinfection among IDU populations.

In many areas of the developing world, the evolving HIV epidemic is clearly associated with injecting drug use and HIV/HCV coinfection rates are high. In Manipur, India, 92 percent of IDUs with HIV infection are coinfecting with HCV [11]. A study of 500 young injectors in Pakistan found HCV and HIV prevalence of 42 percent and 3.4 percent, respectively. High levels of sharing equipment were reported and annual incidence of HCV and HIV in follow-up was 22 percent and 2 percent, respectively [12]. In southern China, levels of HIV and HCV are rapidly rising due to escalating numbers of injecting drug users. In a study of 138 HIV-infected IDUs from Yunnan province, the rate of HCV coinfection was 99 percent [13]. HIV infection was detected in 68 percent of subjects after one year of injection drug use indicating high levels of needle/syringe sharing. A further study of 547 injectors from Guangxi in southern China demonstrated an overall HIV/HCV coinfection rate of 18 percent with 95 percent of HIV-infected users positive for HCV antibodies [14]. In Armenia, where a recent program has been established to provide access to antiretrovirals, 51 percent of patients assessed were coinfecting with HCV [15], and in St Petersburg, Russia, 81 percent of HIV-infected individuals were found to be HCV positive [16]. These high levels of HIV/HCV coinfection are likely to have significant implications for liver-disease morbidity into the future.

## The Effect of HIV on HCV Viral Load, Transmission, and Chronicity

After acute infection, the likelihood of HCV chronicity increases from 70 to 85 percent in HIV uninfected individuals to over 90 percent in HIV-infected individuals, particularly in those with advanced immunosuppression [17–19]. Individuals with HIV/HCV coinfection have been shown to have higher levels of HCV RNA in plasma than those with HCV alone [20–22], and, in some studies, increased levels have been correlated with more advanced immunosuppression [23]. High levels of HCV viremia are likely to result in a greater risk of transmission and reduce therapy success [24]. However, higher HCV viral load in HIV-infected individuals is unlikely to explain greater rates of liver disease progression as there is no correlation between HCV viral load and progression of fibrosis [25].

## Effect of HIV on Liver Disease Progression

There is convincing evidence that coinfection with HIV significantly worsens the prognosis of HCV-related liver disease. Chronic HCV infection may result in cirrhosis, liver failure (end stage liver disease–ESLD), and liver cancer, all of which are associated with high morbidity and mortality. A meta-analysis of eight studies, examining the risk of cirrhosis and ESLD in HIV/HCV coinfecting individuals versus HCV monoinfected individuals, found a twofold and sixfold higher risk of progression to cirrhosis and liver failure, respectively [26]. This meta-analysis included studies of people with haemophilia [27–30], injecting drug users [31;32], and mixed populations [23;33]. Risk factors for liver disease progression in HIV/HCV-coinfecting individuals include heavy alcohol intake, older age (>25 years) at HCV acquisition, and more advanced HIV disease (CD4 count <200–250 cells/ $\mu$ l) [31;34]. Other factors that may increase liver disease progression include increased HCV quasispecies variability [35], occult HBV infection [36], and the effect of antiretroviral therapies on fibrosis [see below]. For a summary of ESLD in HIV/HCV coinfecting individuals, see Appendix 2.

Despite higher rates of liver disease progression in HIV/HCV-coinfecting individuals, the degree of liver inflammation as measured by either liver enzymes or histological activity on liver biopsy is similar to that of HCV-monoinfected individuals. Furthermore, 10 percent of HIV/HCV-coinfecting individuals have normal hepatic enzyme levels (such as ALT), but many of these individuals have significant liver fibrosis [37]. Thus, a normal ALT level should not be used to exclude HIV/HCV-coinfecting individuals from liver biopsy and other assessment for HCV treatment.

## The Effect of HAART on HCV-related Liver Disease Progression

The introduction of highly active antiretroviral therapy (HAART) has markedly reduced HIV-related morbidity and mortality. However, prolonged life expectancy through decreased risk of opportunistic infections has increased the potential for morbidity related to HAART itself or other comorbidities such as viral hepatitis-related liver disease. Non-HIV related conditions such as liver disease constitute an increasing proportion of underlying causes of death among people with HIV.

Studies examining the impact of HAART on liver disease morbidity and mortality in people with HIV/HCV coinfection have reported contrasting findings. An early French study suggested that a HAART regimen including protease inhibitors may delay fibrosis progression, although the mechanisms behind this were not clear [38]. The possibility of a direct benefit of antiretroviral therapy on liver-related pathology has been further supported by other studies, including a cohort study from Germany, which demonstrated a marked reduction in liver related mortality in HIV/HCV-coinfected individuals treated with HAART [39]. A study from France observed a greater degree of fibrosis in HIV/HCV-coinfected individuals with a longer duration between presumed date of HIV infection and commencement of HAART, suggesting that HAART may slow fibrosis progression [40]. Similar data from a recent U.S. study specifically targeting HIV/HCV-coinfected drug users confirmed that less advanced HIV disease, successful antiretroviral therapy (ART) (HIV VL < 75 copies/ml), and non-Hispanic race were associated with a reduced risk of liver disease progression [41]. However, other studies have not confirmed the association between ART and reduced liver fibrosis [42;43]. In a multi-center European study of liver biopsies from 914 HIV/HCV-coinfected individuals, of whom the majority (83 percent) were former IDUs, severe liver fibrosis was correlated with older age, heavy alcohol use (> 50 g/day), and CD4 count less than 500 cells/mm<sup>3</sup>, but *not* with HAART usage [43].

Despite some contrasting findings, it does appear that HAART has reduced both overall and liver disease-related mortality among HIV/HCV-coinfected individuals. The reduction in liver disease morbidity and mortality is despite the well described potential of HAART to cause hepatotoxicity. However, most episodes of hepatotoxicity are without symptoms, short-term, and manageable by either switching of ART agents and/or a period of treatment cessation.

Several studies have examined the effect of commencing HAART on HCV viral load and have yielded conflicting results. Most studies have found no evidence for an effect of HAART on HCV viral load, [44–46] although several have reported significant transient increases after HAART initiation along with elevations in transaminases [47;48]. Despite having little direct effect on HCV viral load, there have been reports of

HCV clearance after the commencement of antiretroviral therapy—presumably through immune mediated mechanisms—but these cases are rare [49].

## Causes of Morbidity and Mortality in HIV/HCV-Coinfected Individuals

The spectrum of morbidity among HIV-infected individuals has changed considerably since the era of HAART. This changing spectrum has included an increase in the importance of non-HIV-related conditions, such as chronic liver disease. In one U.S. study, HCV became the leading cause of death in HIV-infected individuals, with end-stage liver disease contributing to 50 percent of all deaths during the late 1990s [50]. Similar high rates of hospital admission and deaths from liver disease have been reported from other countries with significant rates of HIV/HCV coinfection, such as Spain [51]. In a French HIV-infected cohort [52], among 265 deaths reported in 2001, 49 percent were related to AIDS, 14 percent to ESLD and 37 percent to other causes. In this cohort, deaths from ESLD increased from 1.5 percent in 1995 to 14 percent in 2001. In another French cohort, liver disease was the most common cause of death in HIV/HCV-coinfected individuals; nearly 40 percent of these deaths occurred despite a CD4 count > 200 cells/mm<sup>3</sup> [53].

Although morbidity from liver disease is relatively common among HIV/HCV-coinfected individuals, other non-HIV-related morbidity and mortality is prominent in some settings, particularly those with large numbers of active IDUs. Among more than 1,000 people followed for more than two years in the Swiss HIV cohort [5], end-stage liver disease accounted for between 6 and 11 percent of deaths in the HCV/HIV coinfecting population, whereas HIV-related deaths and overdose of narcotic drugs contributed to mortality rates of 40 and 11 percent, respectively, in this group.

## End-Stage Liver Disease among HIV/HCV-Coinfected Individuals

Once HIV/HCV coinfecting individuals have developed cirrhosis, the risk of decompensation (liver failure) is considerably higher than for HCV-monoinfected individuals. Survival after liver decompensation is poor, at around 35 percent at one year, and 11 percent at two years, and there is little evidence that this has improved at all in the HAART era [54;55].

Evidence is also now emerging that risk of liver cancer in HCV-infected individuals may be increased with HIV coinfection. In a Spanish study of 7 HIV/HCV-coinfected and 31 HCV-monoinfected individuals with liver cancer, those with coinfection were diagnosed at a younger age and with a shorter duration of HCV infection [56]. A retrospective review of 160 liver cancer cases in the United States and Canada (41 HIV/HCV-coinfected and 119 HCV-monoinfected) also showed a shorter duration of HCV infection (26 versus 35 years), and a younger mean age at diagnosis (52 versus 61 years), in the HIV/HCV-coinfected individuals. Survival was poor in both HIV/HCV-coinfected and HCV-monoinfected individuals with liver cancer [57].

For HIV/HCV-coinfected individuals with end-stage liver disease, the only effective treatment option is liver transplantation. Transplantation for HIV/HCV-coinfected individuals has gradually become more widespread in recent years and several small case series have reported their outcomes [58–60]. Since the advent of HAART, survival has been similar in HCV-monoinfected and HIV/HCV-coinfected individuals, with the main cause of death related to aggressive post-transplant HCV reinfection and cirrhosis. Loss of HIV control and AIDS-related infections are unusual, although generally HIV/HCV-coinfected individuals with advanced HIV disease (CD4 count < 100/mm<sup>3</sup> or active opportunistic infections) are excluded from transplantation. Furthermore, a higher proportion of HIV/HCV-coinfected individuals with end-stage liver disease die while waiting for transplants, possibly due to the more rapid course of deterioration.

## The Impact of HCV on HIV Disease Progression

The issue of whether coinfection with HCV has a negative impact on HIV disease progression remains controversial, despite an increasing number of studies examining this issue. HCV infection may affect HIV disease outcomes, either by directly hastening progression to AIDS or death, or by affecting adequate immune reconstitution after HAART, and studies have looked at one or both of these measurements [see Appendix 3 for a summary of HCV impact on HIV disease progression].

Comparison of HIV disease outcomes in HIV-monoinfected and HIV/HCV-coinfected populations is complicated by significant differences in demographic and behavioral characteristics between groups. HIV risk factor distributions differ considerably, with sexual acquisition predominating among HIV-monoinfected populations, and injecting drug use predominating among HIV/HCV-coinfected populations [61;62]. Attitudes and adherence patterns to antiretroviral therapy may also differ between HIV-monoinfected and HIV/HCV-coinfected populations [63]. Failure to properly control for these differences has a marked impact on study findings.

In addition, HAART itself has an obvious significant effect on HIV-related morbidity and mortality and different studies have been conducted in the pre-HAART era, the post-HAART era, or a mixture of both. In the pre-HAART era, several longitudinal and cross-sectional studies failed to show a significant effect of HCV on HIV progression [64–66], whereas others were able to demonstrate a more rapid clinical progression to AIDS in HIV/HCV-coinfected individuals [67].

In recent years, since the widespread use of HAART, there have been many more reports of the effect of HCV coinfection on HIV disease progression, but findings still remain discordant. Several studies have found no association between HIV/HCV coinfection and poorer HIV disease outcomes. In 2002, a U.S. study in more than 1900 HIV-infected individuals demonstrated no differences between HIV-monoinfected and HIV/HCV-coinfected populations with regard to incidence of AIDS, death or decline in CD4 count over time [68]. In particular, CD4 cell count rise after HAART was not affected by presence of HCV coinfection. However, HIV/HCV-coinfected individuals were less likely to be prescribed HAART. A more recent report from a European cohort study, EuroSIDA, examined survival, HIV disease progression, and virological and immunological response in almost 6000 individuals, of whom 33 percent were HIV/HCV coinfected [9]. HIV/HCV-coinfected individuals had an expected, much higher rate of liver-related deaths, but there was no increased risk of AIDS, and overall mortality rates were similar to HIV-monoinfected individuals. There were also no differences between the two groups in HIV virological suppression or CD4 count response following HAART. Although HIV/HCV-coinfected individuals were less likely to be prescribed HAART, HAART was initiated at a similar baseline CD4 count between groups (between 200 and 250 cells/mm<sup>3</sup>), and similar regimens were used. In the Women and Infants Transmission Study, 652 HIV-positive women—29 percent coinfected—were followed with respect to progression to a first AIDS-defining illness. The rate of clinical progression was similar among HIV-monoinfected and HIV/HCV-coinfected women [69].

In one of the few studies from a developing country, the Thai HIV-NAT cohort, the impact of HCV infection among patients who initiated ART was studied [70]. Prevalence of HCV was low, at 7 percent, and no significant difference in the rate of progression to AIDS or death was seen between HIV-monoinfected and HIV/HCV-coinfected groups over the initial 48 weeks of ART. There was some evidence of lower CD4 count responses in the HIV/HCV-coinfected group at week 4, but by week 48 these differences had resolved. Similarly, in another Asian study from Taiwan, with a relatively low HCV coinfection prevalence rate (12 percent), no adverse effect of coinfection was noted on virological suppression or immunological recovery [71].

The studies described above, including some with very large study populations, have found limited, if any, impact of HCV coinfection on HIV outcomes. Yet there have been several studies with contrasting findings. In 2002, the Swiss HIV Cohort

Study demonstrated, in a population on HAART, a slightly greater risk of progression to AIDS or death in those with HCV coinfection than those without. They also found more rapid HIV disease progression among individuals with active injecting drug use [5]. Despite similar virological responses, HIV/HCV-coinfected individuals were also less likely to achieve a CD<sub>4</sub> cell increase of at least 50 cells/mm<sup>3</sup> by one year after starting HAART. The authors postulated that this may be due to some direct immunological effect of HCV on CD<sub>4</sub> cells. Similarly, in the U.S.-based HIV Atlanta VA Cohort Study (HAVACS), involving a high proportion of black injecting drug users, HIV/HCV-coinfected individuals were shown to have shorter durations of survival from HIV infection or AIDS diagnosis [72]. HIV/HCV-coinfected subjects were less likely to be prescribed HAART, but in this study no evidence of altered CD<sub>4</sub> cell responses after HAART initiation were seen. In a further cohort study of more than 2000 HIV-positive persons (6 percent HCV-coinfected) from a central London clinic, the likelihood of an initial AIDS-defining illness, or a CD<sub>4</sub> count less than 200 cells/mm<sup>3</sup>, was found to be increased in HIV/HCV-coinfected individuals, despite no evidence of lower CD<sub>4</sub> count responses in the coinfecting group [73].

Differences in antiretroviral history, including time spent on treatment and regimens used, may explain many of the differences seen between monoinfected and coinfecting groups. In an Italian cohort study, where the rate of HIV/HCV coinfection was over 50 percent, HCV infection had no effect on progression to AIDS in the pre-HAART era, but in the HAART era the risk increased significantly [74]. This was partly accounted for by a significantly lower time spent on HAART in the HIV/HCV-coinfecting group. Both real difficulties in managing HAART-related hepatotoxicity in HCV-infected individuals and perceived difficulties resulting in a reluctance or delay to start HAART, particularly for those who are injecting drug users, may account for much of the suggested increased morbidity in HIV/HCV-coinfecting patients.

Even in those individuals who do initiate HAART, the issue of whether CD<sub>4</sub> count response is impaired also remains ambiguous. Despite several large cohort studies in diverse populations demonstrating no appreciable differences between HIV-monoinfected and HIV/HCV-coinfecting groups [9;68], a recent meta-analysis designed to look at this question concluded that, as determined by CD<sub>4</sub> cell count at 48 weeks of HAART, HIV/HCV-coinfecting individuals did have a lower level of immune reconstitution, with a mean increase of 33 cell/mm<sup>3</sup> less than that of HIV-monoinfected individuals [75].

In sum, it remains to be clarified whether HCV does indeed have a negative impact on HIV disease progression in the era of effective HAART, or whether the findings in those studies reporting a positive association simply represent inherent differences in the groups studied, altered patterns of antiretroviral use, and other unidentified bias. It is notable that almost all the studies so far lack adequate data on HCV determinants, such as HCV genotype and viral load, levels of transaminases, liver biopsy findings, and

HCV treatment details. All of these variables are likely to have significant impact, not only on liver disease progression and HAART-related hepatotoxicity, but may also impact HIV disease progression. There are certainly biologically plausible reasons why HCV could negatively impact CD4 cell numbers and function [76–78]. Further elucidation of the virological and immunological mechanisms of HIV-HCV interactions, alongside continuing feedback from long-term prospective cohorts, will be of value.

## Conclusion

There remain uncertainties regarding the true impact of coinfection with HIV and HCV on the progression and outcomes of these infections. This is largely due to difficulties in performing accurate natural history studies, particularly in the constantly developing fields of HIV and HCV medicine. Still, it seems certain that the presence of HIV infection, especially when associated with significant immunosuppression, has a negative impact on HCV-related disease progression, and results in an increase in liver-related morbidity and mortality from conditions such as cirrhosis and liver cancer. This is of particular concern for areas of the world where the HIV epidemic is fuelled by recent increases in injecting drug use, and where rates of HCV coinfection are likely to be high. The extent to which this can be avoided will depend both on the continuing successful treatment of HIV infection and the early identification and, where possible, successful treatment of HCV infection. Whether the presence of HCV coinfection worsens the prognosis of HIV infection is less clear at present. There is some evidence to suggest that the coexistence of HIV/HCV may impact CD4 count recovery, and there are undoubtedly immunological interactions between these viruses that have yet to be elucidated. The relationship between these and any negative effect on clinical HIV outcomes remains to be seen, and will only become clearer with further follow-up and continuing research. On a positive note, there is good evidence that achieving satisfactory virological and immunological responses to HAART is possible for the majority of HIV/HCV-coinfected patients, including those who are injecting drug users, and that successful ART in this population is likely to reduce liver disease progression [41]. The combination of effective HAART, increasing use of anti-HCV treatment, and greater clinician expertise in the management of HIV/HCV coinfection is likely to significantly reduce liver-disease related mortality in the future.

# Appendices

## Appendix 1

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### Impact of HIV on HCV disease

- ▶ Increased likelihood of chronicity after acute HCV infection
  - ▶ Increased HCV RNA levels in chronic infection
  - ▶ Significantly increased risk of progression to cirrhosis and liver failure
  - ▶ Greater fibrosis progression in those with more advanced immunosuppression
  - ▶ Likelihood of lesser fibrosis development in individuals treated successfully with HAART
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## Appendix 2

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### End-stage liver disease (ESLD) in HIV/HCV-coinfected individuals

- ▶ ESLD is now one of the leading causes of ill health and death in HIV/HCV-coinfected individuals
  - ▶ HIV coinfection hastens time to first episode of decompensation after cirrhosis development
  - ▶ Liver cancer in HIV/HCV-infected individuals occurs after a shorter duration of HCV infection and at a younger age than in HCV-monoinfected individuals
  - ▶ Liver transplantation is increasingly performed in the setting of HIV/HCV coinfection
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## Appendix 3

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### Impact of HCV on HIV disease progression

- ▶ Conflicting evidence regarding the effect of HCV infection on HIV disease progression in both pre- and post-HAART eras
  - ▶ Significant differences in patterns of HAART usage, toxicity, and population characteristics may account for many of the differences in HIV-related survival reported in studies
  - ▶ No evidence for impairment of HIV virological suppression after HAART commencement in HCV-positive individuals
  - ▶ Potential blunting of CD4 count response (approx. 33–50 cells/mm<sup>3</sup> less at 48 w) after HAART initiation in some studies
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Chronic HCV infection is one of the most significant public health problems among HIV-seropositive, drug-involved populations... Given the large numbers of coinfecting IDUs worldwide, the question of whether to address HCV in HIV-coinfecting IDUs is moot. The more apt question is how to do so most effectively.

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# Limiting Harm from Chronic Hepatitis C Infection for HIV-Positive People with Drug Dependency: Prevention and Treatment

Lynn E. Taylor, Beth Schwartzapfel, and Pierre M. Gholam\*

## Introduction

Chronic hepatitis C virus (HCV) is a worldwide pandemic, with an estimated 170 to 400 million persons infected globally [1]. An estimated 4 to 5 million of these are coinfecting with HIV and HCV [2]. In countries with widespread access to highly active

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antiretroviral therapy (HAART), HCV has become a leading cause of cirrhosis, liver failure, hepatocellular carcinoma (HCC), and death among human immunodeficiency virus (HIV)-seropositive persons [3–6]. In the developing world, tuberculosis and other opportunistic infections remain the leading cause of death among HIV-seropositive persons [7–10]; however, with growing availability of generic antiretroviral medications [11], chronic illnesses such as HCV will increasingly become a pressing issue.

HCV prevalence among persons with HIV varies greatly by region and by HIV risk factor (see table at end of article). These disparities are likely due to varying cohort characteristics, as well as inconsistent data collection methods.

Chronic HCV infection is one of the most significant public health problems among HIV-seropositive, drug-involved populations. While HCV prevalence among general populations of HIV-seropositive persons varies, prevalence among HIV-seropositive injection drug users (IDUs) is consistently high. Among cohorts of HIV-seropositive IDUs, prevalence ranges from 70 to 90 percent [12;14;15;22;23]. One study in Brazil found an 85 percent prevalence among HIV-seropositive IDUs, and a study of IDUs in Southern China found that 95 percent of HIV-seropositive (as opposed to 70 percent of HIV-seronegative) participants were HCV-infected [24]. Additionally, a study of young IDUs in Vancouver, Canada, found an incidence of HIV/HCV coinfection of 5.2 per 100 person-years [23].

## Prevention

Given that most HIV-seropositive IDUs are infected with HCV, the focus of prevention efforts must be threefold: first, drug users who do not inject and persons who have just begun injecting must be targeted for primary prevention. There is only a small window for intervention before new injectors become HCV-seropositive [23]. Second, the sexual and drug-using partners of coinfecting IDUs must be targeted for prevention. Third, HIV-seropositive IDUs already infected with HCV must have access to care to help slow disease progression. An essential element of all of these strategies is identification of persons with HCV, by means of accessible HCV testing [25;26]. Widespread HCV prevention would benefit the individual and public health through reductions in disease acquisition, spread of established infection, and morbidity and mortality.

In order to build effective prevention programs, health care providers must first have access to communities of IDUs, and IDUs must have access to health care. A myriad of socioeconomic and institutional barriers prevent delivery of care to this population. Given the illicit nature of drug use and the stigma IDUs face, many are reluctant to come into contact with the health care system, or face logistical challenges accessing health

care (such as lack of transportation or health insurance) [27–29]. Many physicians are misinformed about substance use; a recent U.S.-based survey of primary care physicians found that substance abuse-related training in medical schools and continuing education is not adequate [30]. At worst, physicians are openly hostile to drug users, which has negative consequences for patients' health and well-being [31]; inequities in health systems and biases in practice have led to inferior care and outcomes for many IDUs [32–36]. In order to gain trust and credibility with individuals who may be living on the margins of society, medical providers must employ a compassionate, nonjudgmental approach to care [37;38].

### **HCV testing**

Of the estimated 4 million people infected with HCV in the United States, approximately 50 percent are unaware of their infection [39]; many IDUs in particular are not aware of their status [40]. Increased screening and knowledge of HCV status decreases HCV transmission [40;41] because persons who know their HCV status are less likely to engage in HCV risk behaviors [40]. HCV-seropositive persons who engage in care early can be vaccinated against hepatitis A virus (HAV) and hepatitis B virus (HBV), counseled on alcohol reduction or cessation, educated about how not to transmit infection, and medically monitored. Diagnosis and treatment of commonly co-existing depression and other psychiatric disorders may lead to a decrease in risk-taking behaviors that further HCV and HIV spread or acquisition of other infections, and may permit eventual interferon-based therapy which is contraindicated in the setting of untreated severe psychiatric illness.

Free or low-cost, low-threshold, anonymous HIV testing is widely available in the United States [42]. Unfortunately, no such system exists for HCV. Integrating HCV testing into the HIV testing infrastructure would be a sensible and much needed policy, as the target populations overlap and integration can conserve resources.

All HIV-seropositive persons should be tested for HCV, though the optimal frequency of testing in the presence of ongoing risk factors has not been established [43]. Accessible HCV testing for partners of coinfecting IDUs is another critical step. Drug-using partners of HCV-positive persons are at high risk for HCV, and should be tested at regular intervals [25], though the optimal frequency for testing is not clear. Heterosexual transmission of HCV among long-term, monogamous, serodiscordant couples appears to be low [44–47]. Consequently, the U.S. Centers for Disease Control and Prevention (CDC) considers HCV testing among long-term steady partners of HCV-positive persons to be “of uncertain need” [25]. Risk of sexual transmission in the setting of multiple sexual partners appears to be higher [48;49], perhaps due to concomitant sexually transmitted diseases (STDs), though HCV testing for persons with a history of multiple sex partners or STDs is likewise considered to be “of uncertain need” [25]. Early reports seemed to indicate that risk of sexual transmission was low among men who have sex

with men (MSM) [50]. A recent rash of outbreaks of acute HCV among communities of HIV-seropositive MSMs may indicate otherwise [43;51–56], though the evidence is not conclusive [57;58].

### **Prevention of HCV acquisition among HIV-seropositive IDUs**

Cessation or reduction of injecting is the most straightforward HCV prevention strategy. Substance abuse treatment has been shown to reduce the incidence of HCV [59], HIV [60], and high-risk behavior [61], and to promote adherence to, and efficacy of, both HIV and HCV treatments [62–64]. Conversely, *without* access to addiction treatment, HIV-seropositive drug users often have difficulty accessing care and adhering to therapies [65–71].

Among IDUs who are not able or willing to stop injecting, the most salient issues for prevention of HCV transmission are access to sterile syringes and education about safer injection practices [72–74]. With the advent of such prevention-minded policies as syringe exchange [38], physician syringe prescription [75], over-the-counter pharmacy syringe sales [76–79], medically supervised injection facilities [80–82], and heroin prescription [83;84], drug injection is not necessarily associated with exposure to parenterally transmitted infections [85;86].

Injecting drugs involves many steps and components that may pose an HCV transmission risk [87;88], and a harm reduction approach must take each step into account. In preparing drugs, IDUs often liquefy powder or tar heroin by mixing it with water (with or without heating it under a flame), a process known as “cooking,” and then draw the liquid into a syringe through a cotton filter. Risk for HCV has been shown to be associated with sharing water, cottons, and cookers [89;90]. Further, when multiple individuals are injecting together, a single syringe is often used to measure the drug; the drug is then apportioned from the single syringe into multiple syringes (a process known as “backloading”), or back into the cooker to be drawn up individually. If the syringe used to divide the drug is not sterile, all of the persons are at risk for HCV, even if they each use a new, sterile syringe [89]. Other practices among IDUs, such as “booting” or “jacking,” wherein a person draws blood into his/her syringe before injecting, may also increase HCV risk [91]. Factors such as whether the injector is “dopesick” (in withdrawal) at the time of injection, or whether the injection takes place in a private, secure area (versus a public place such as a car or shooting gallery) also influence risk [89;92].

Noninjecting drug-related HCV risks must also be considered [93]. In particular, sharing straws to snort cocaine and sharing pipes to smoke crack cocaine can provide means of transmission due to intranasal irritation and cracked, burned, or bleeding lips [94;95]. High-risk sexual behavior, such as selling sex or trading sex for drugs, which often accompanies illicit drug use, has also been found to be an independent risk factor for HCV infection [90].

Interventions targeted at IDUs work best when they are integrated into other settings frequented by drug users, such as drug treatment centers and correctional institutions [96–100]. Integration of HCV prevention education into a drug treatment facility has been found to be effective in reducing risk behaviors [101]. Evidence-based HCV prevention programs among IDUs are not yet as established as those for HIV prevention. However, in the absence of these data, the existing HIV prevention literature can be utilized to extrapolate that culturally appropriate, community-based, and peer-driven interventions for the prevention of HCV among drug users are feasible and effective in a wide range of settings in both the industrialized [102–104] and developing world [105].

### **Preventing transmission to social, sexual, and drug-using networks**

The primary prevention strategy for partners of coinfecting IDUs is access to HCV testing (as described above). Using social networking to identify persons at high risk has been an effective method in the setting of other infectious diseases, such as syphilis [106]. The CDC recently reported on an effective multi-site pilot program in which HIV-seropositive persons and high-risk HIV-negative persons recruited members of their social networks for HIV testing [58]. Some have proposed monetary incentives for IDUs who are able to engage their partners in care [107]; the abovementioned CDC pilot included small incentives for recruiters. Once engaged in care, HCV prevention among partners of coinfecting persons, like that among coinfecting IDUs themselves, must be centered on low-threshold, nonjudgmental care, access to sterile syringes, and education about safe injection practices (as described above).

Household and intrafamilial transmission of HCV appears to be rare, even in the setting of HIV/HCV coinfection [108]. A recent Egyptian study found a strong link between HCV-seropositivity and having an HCV-seropositive family member [109]. However, the evidence in these cases seemed to suggest that multiple HCV-positive family members were infected by the same source, usually health care-related injections with nonsterile syringes, rather than via one index case infecting other family members. Nevertheless, it makes good practical sense to advise HIV-seropositive persons coinfecting with HCV not to share personal care items (such as toothbrushes, razors, and nail clippers), which may contain HCV-infected blood.

### **Preventing perinatal transmission of HCV infection**

Vertical transmission of HCV infection is well documented. One widely quoted study reports HCV viremia (as measured by HCV RNA PCR) in approximately 5.6 percent of infants born to HCV-seropositive mothers. In this and other analyses, risk of transmission appears to increase as maternal HCV viral load increases [110–112] although this has not been supported by all studies [113;114]. Multiple studies limited by small numbers and lack of long term follow-up suggest that among HCV/HIV-coinfecting mothers, the

risk of vertical transmission is higher than that in mothers with HCV monoinfection, with some reporting rates of transmission as high as 40 percent [115–117]HCV. In one meta-analysis including 2382 infants from 10 studies of HCV-infected women with and without concomitant HIV infection, the estimated odds ratio of HCV vertical transmission was 2.82 from HCV/HIV-seropositive mothers compared with HCV-seropositive mothers. In a subanalysis of 1327 infants born to viremic (HCV RNA positive) mothers, the risk estimate of HCV vertical transmission was 1.97 from HCV viremic/HIV-seropositive coinfecting mothers compared with HCV viremic/HIV-seronegative mothers [118]. IDU has also been reported to be a risk factor for vertical transmission of HCV in some studies [114] but not in others [113;119;120]. Prolonged duration between rupture of membranes and delivery has also been suggested as a potential risk factor for HCV transmission [120].

Breastfeeding does not increase the risk of HCV transmission to newborns [121;122]. However, in regions of the world where HIV-seropositive mothers have access to adequate health care, clean water, and breast milk substitutes, they are advised not to breastfeed their infants due to the risk of HIV transmission [123]. In areas of the world where HIV-seropositive mothers do not have access to adequate health care, clean water, and breast milk substitutes, with increased risk of other infectious diseases and nutritional deficiencies resulting in elevated infant death rates, the mortality risks associated with artificial feeding may outweigh the possible risks of acquiring HIV infection [124].

Factors reducing the transmission of perinatal HCV transmission have been the focus of few studies conducted mostly in HCV-monoinfected populations. Overall, preventive measures should focus on improving maternal health and preventing behaviors that may adversely impact fetal outcomes such as heroin, cocaine, tobacco, and alcohol use during gestation. Our current state of knowledge does not support elective Caesarian section [125], or delaying pregnancy until a course of HCV therapy is pursued. Since current HCV-antiviral therapies are contraindicated during gestation and up to six months prior to pregnancy due to teratogenicity, their impact on preventing perinatal transmission cannot be safely evaluated.

### **Halting or slowing HCV disease progression**

The literature remains contradictory regarding the impact of HCV on HIV disease progression [126;127]. However, it is clear that HCV disease progression is accelerated in persons with concomitant HIV infection [128–131]. Therefore slowing or halting disease progression is especially critical in coinfecting persons.

For coinfecting IDUs, managing multiple comorbidities can be an overwhelming proposition. Fortunately, IDUs who work with their physicians to carefully manage and control their HIV infection are, to a certain extent, already addressing management of

their HCV infection, and should be encouraged as such. Because liver disease is accelerated in the presence of HIV [132], with higher degrees of fibrosis associated with greater degrees of HIV-induced immunosuppression [133], immune restoration with the addition of HAART is thought to slow the natural disease course of HCV and reduce liver-related morbidity and mortality. Several studies suggest a long-term positive effect of HAART on HCV disease course [134–137]. Earlier HAART initiation may benefit coinfecting patients by delaying HCV-related fibrosis progression [138]. These initial, retrospective reports are encouraging, and further prospective studies are warranted.

Abstinence from alcohol use is another important component of preventing disease progression among coinfecting persons. Prevalence of HCV is increased among alcoholic patients [139–142]. Heavy drinking (usually defined as  $\geq 50$  g of alcohol daily) promotes fibrosis progression and increases risk for cirrhosis and HCC among persons with HCV [142–147]. Even mild to moderate alcohol consumption has been shown to have a deleterious effect on HCV disease progression, though there is not consensus on what constitutes “mild to moderate” drinking; various studies have used such disparate cutoffs as 30–40 g/day [148],  $\leq 50$  g/day [149], 10 g/day [150], and  $< 140$  g/week [151]. Further, alcohol use may decrease the likelihood of spontaneous viral clearance during primary infection [152], and may decrease the efficacy of anti-HCV therapy [142]. Important questions regarding HCV and alcohol use remain. What role does HIV play? Do different patterns of drinking differently impact HCV disease progression? Given that it is impossible to counsel coinfecting patients on what, if anything, constitutes a “safe” level of alcohol consumption, the most accurate information is that eliminating alcohol use entirely is the safest course. Advocating a reduction in alcohol use when cessation is not possible is a reasonable harm reduction approach.

Another means to prevent additional hepatic injury among coinfecting persons is vaccination against other viral hepatitis infections. Because of overlapping risk factors for acquisition, risk of fulminant hepatic failure due to superinfection with HAV [153] and more rapid liver disease progression in the presence of HBV [154], all coinfecting persons should be vaccinated against HAV and HBV if susceptible [43;155;156]. There is some concern that HIV-seropositive persons demonstrate reduced immunogenicity to these vaccines; a recent retrospective analysis of HAV vaccination in HIV-seropositive persons found a response rate of only 48 percent (as compared to 100 percent in HIV-negative populations), with higher CD4 count being an independent predictor of immunogenicity [157]. Although some vaccine recommendations for HIV-positive persons, such as those for pneumococcal vaccine, vary with CD4 count, no guidelines currently suggest changing clinical practice regarding HAV or HBV vaccine administration for HIV-positive persons [156].

While these strategies may help delay or reduce the severity of progression of HCV-induced liver disease, it is reasonable to assume that they would likely optimize patients

for candidacy for HCV therapy. Achievement of a sustained virological response (SVR), which achieves permanent viral clearance, halts further inflammation and fibrosis in the liver and has been shown in some studies to result in a regression of liver fibrosis. In addition to its role in preventing disease progression among persons already infected with HCV, HCV pharmacotherapy can be viewed as a means to prevent HCV disease transmission, as a person who has achieved SVR cannot transmit HCV (unless he/she is re-infected).

### **Hepatotoxicity**

Addressing hepatotoxicity among coinfecting patients is another important element of care. Hepatotoxicity in the HAART era is one of the most commonly encountered adverse events in persons living with HIV in general, and HCV/HIV coinfection in particular. Studies from Spain and Thailand have identified HCV coinfection as well as alcohol intake and HBV coinfection as independent risk factors for HAART-associated hepatotoxicity [158;159]. While liver enzyme elevation is common among patients initiating HAART, clinical hepatitis and life-threatening HAART-related hepatotoxicity are rare. However, HCV coinfection increases the rate of liver enzyme elevation and the rate of severe hepatotoxicity [160], and has been found to decrease tolerability of HAART [161]. Among HCV/HIV-coinfecting subjects, one large retrospective Italian study found that the incidence of severe hepatotoxicity was 17.71 per 100 patient-years of follow up in a HAART-naive patient group and 8.22 per 100 patient-years in a HAART-experienced group [162]. In addition, HAART-associated hepatotoxicity appears to correlate with the severity of liver fibrosis in coinfecting persons [163].

The contribution of different classes of antiretroviral agents to hepatic injury continues to be the subject of some controversy and all antiretroviral medications have been implicated. Many studies have linked the non-nucleoside reverse transcriptase inhibitors nevirapine and efavirenz and the protease inhibitor ritonavir at full dose with severe hepatic injury, particularly in the setting of concomitant viral hepatitis [160;164]. As HCV infection appears to be an independent risk factor for antiretroviral-related hepatotoxicity, preliminary evidence has emerged suggesting that pretreatment of HCV in coinfecting individuals may reduce the hepatotoxicity associated with subsequent antiretroviral therapy [165].

HCV/HIV-coinfecting persons with concomitant drug use are also at risk of hepatotoxic injury related to heroin [166], cocaine [167], and amphetamines [168]. Individuals with comorbid psychiatric illness with access to psychiatric pharmacotherapy are at risk for hepatotoxicity related to selective serotonin reuptake inhibitors [169], tricyclic antidepressants [170], and antipsychotics [171]. Finally, antituberculous regimens have well documented liver toxicities which may be more prominent in persons with AIDS, particularly in persons coinfecting with HCV [172;173].

## Treatment

When HCV first emerged as a widespread infectious disease in the early 1990s, the only treatment available was interferon (IFN) monotherapy. This was initially administered for 24 weeks, with an efficacy rate of roughly 6 percent [174;175]. When the length of treatment was extended to 48 weeks, SVR rates improved to 13 percent [176], but it was not until ribavirin (RBV) was added in 1998 that efficacy rates increased substantially, to 41 percent [177]. With the advent of pegylated IFN (peg-IFN) in combination with RBV, SVR rates in monoinfected patients are now above 50 percent [177;178].

To date, there have been three major prospective, randomized, controlled trials (two national, one international) of peg-IFN plus RBV in coinfecting patients. The trials demonstrated that this regimen is relatively well-tolerated and effective in HIV-infected individuals [179–181], albeit less effective than in HCV-monoinfected persons, with overall SVR rates between 27 and 40 percent. Two of these studies demonstrated histological response in 35 percent and 43 percent of virologic nonresponders, respectively [182;183].

Knowledge of the more aggressive HCV disease course in the setting of HIV and recent treatment data for coinfecting individuals have led to the development of several sets of evidence-based anti-HCV treatment guidelines for coinfecting persons [13;43;184–186]. These guidelines indicate that peg-IFN plus RBV for 48 weeks, irrespective of genotype, is now the initial pharmacologic treatment of HCV among coinfecting patients [185] (See figure at end of article for treatment algorithm). Ideally, all coinfecting persons should be considered for antiviral treatment. The primary goal of therapy is to eradicate HCV by achieving SVR. While SVR is the desired treatment outcome, the hope of histological and clinical improvement even without SVR may provide sufficient rationale for treatment, and is not necessarily dependent on CD4+ cell count [182;183]. A further goal specific to HIV-seropositive populations is to suppress HCV disease activity to prevent HAART-related hepatotoxicity.

Coinfecting individuals undergoing HCV treatment should be closely monitored due to the potential for adverse events. These can range from mild to life threatening, and may include cytopenias, flu-like symptoms, and depression with suicidality. It bears noting that the combination of RBV and the nucleoside analogue reverse transcriptase inhibitor didanosine (ddI) should be avoided due to the potential for mitochondrial toxicity which can be accompanied by lactic acidosis, pancreatitis, and hepatic failure [187]. Because zidovudine (AZT)-related anemia can be compounded by RBV, individuals taking this combination should be monitored closely for resultant anemia, with the addition of erythropoietin to stimulate red blood cell development if available. Other measures include dose reduction of RBV (which diminishes treatment efficacy) or switching to an alternate antiretroviral agent [188;189] if anemia develops. Peg-IFN/RBV

does not appear to have a negative impact on control of HIV. Individuals with detectable HIV RNA at baseline receiving peg-IFN experience a reduction in HIV RNA [186], and the interferon-induced reduction in absolute CD4+ cell count does not impact stability of the CD4+ cell percentage nor lead to development of opportunistic infections [186]. HIV PVL and CD4+ cell counts return to baseline levels within several weeks of treatment cessation.

Especially in developing countries, access to HCV treatments and laboratory tests needed to administer them safely and effectively, which can cost upwards of U.S. \$20,000 per treatment course, is a major barrier. Recognizing that HCV is an opportunistic infection among persons with HIV [190], many U.S. AIDS Drug Assistance Programs are adding peg-IFN/RBV to their formularies; yet even these programs are often not able to afford the medications. Generic formulations of RBV, but not IFN, are available. Despite their high cost, these medications have been found to be cost-effective in both HIV-coinfected and HCV-monoinfected patients [191–193].

Given a relatively low SVR among coinfecting patients, (especially those with genotype 1, the most common genotype among HIV-seropositive IDUs in many parts of the world), management of patients who do not achieve SVR on peg-IFN/RBV will be essential. Long term maintenance therapy with low-dose peg-IFN in the subset of patients with advanced liver fibrosis or cirrhosis is a promising approach that is currently being investigated in a large, multicenter NIH-funded trial [194;195]. New HCV therapies are in development, and medications intended to be used instead of RBV as adjunctive therapy to IFN will likely be available sooner than medications intended to be used independently, such as HCV protease inhibitors. Adjunctive therapies and antifibrotics are currently being investigated and may be available to coinfecting individuals in the future [196].

### **Complementary and alternative medicine (CAM)**

Given financial barriers and other factors, many persons with HCV are turning to CAM [197]. In particular, the milk thistle plant and its active ingredient, silymarin, have been the subject of some attention with regards to liver health. In vitro and animal studies, as well as small clinical trials among patients with liver disease of varying etiologies, have found minor improvements in liver health and cell growth, and some inhibition of inflammation with the use of these therapies [198–206]. However, meta-analyses which incorporate larger numbers of patients and implement standards for trial quality, have found little benefit [207–209]. The only large-scale, randomized double-blinded trial of silymarin to date, which involved 144 persons with HCV in Egypt, found overall improvements in health and well-being, but no improvements in any HCV-related endpoints [210]. The U.S. National Institutes of Health recently allocated U.S. \$5–6 million for phase I/II clinical trials of silymarin for liver diseases.

Critics warn that CAM is often not subject to the same scientific scrutiny as is its allopathic counterpart [211;212], and thus can be ineffective at best, and harmful at worst. Silymarin, at least, appears to be safe, if not particularly effective, in people with liver disease (unlike other alternative therapies that have been advocated for treatment of HCV, such as colloidal silver, which is known to be poisonous to humans [213;214]). However, studies have found an increasing number of persons with HCV using CAM, with only a small proportion informing their physicians [215]; thus, regardless of its efficacy, physicians must be informed about CAM use and potential side effects [216], including interactions with HAART medications [217;218].

### **Exclusion of IDUs from treatment with peg-IFN/RBV**

Many HCV treatment protocols exclude individuals with substance use [97;219–223], and HCV experts long advocated six months or more of abstinence before treatment with IFN [221;224–227]. This is despite the fact that there is no evidence to support withholding HCV treatment from drug users per se [226;228]. Though newer recommendations now advocate a case-by-case approach for HCV treatment in IDUs [229], many prejudices and misunderstandings remain. Concerns about treating these patients include the potential for reinfection, poor adherence, and psychiatric decompensation or drug relapse[97;226].

Concerns about reinfection are not supported by available evidence. Long-term follow-up studies of IDUs after successful HCV viral clearance have shown very few instances of reinfection [230;231]. While adherence to anti-HCV medications optimizes outcomes [232], substance use itself does not necessarily predict lack of adherence. Physicians are notoriously bad predictors of which patients will adhere to medical treatments, and strategies targeting drug users can maximize adherence [226;233;234]. Instead of assuming that persons who inject drugs will not adhere to HCV therapy, a better gauge by which to judge individual patients may be whether they can adhere to appointments and other medications. For example, in a trial of HCV treatment in persons on methadone, at least 75 percent attendance at weekly clinics for two or more months was required before patients were eligible for treatment [235]. While IFN is known to cause adverse psychiatric events, recent experience reveals that many persons with depression or other psychiatric disorders can be treated with appropriate supports [228;236–239].

In the early days of antiretroviral therapy for HIV, physicians were often reluctant to prescribe life-saving antiretrovirals to drug users and persons with mental illness because of fears of non-adherence and the development of drug resistance [240]. However, in the context of programs that specifically address the unique needs of these populations [241], drug users and persons with psychiatric illness are treated for HIV consistently, safely, and successfully. The lessons learned from the HIV epidemic are applicable with HCV. Multidisciplinary care, which integrates care for HIV, HCV, and

addiction, as well as other services, is the most promising model for successful treatment of coinfecting IDUs [38;62-64;96;97;226;242-247]. In addition to providing low-threshold, “one-stop shopping,” multidisciplinary care precludes the need for referrals to specialists; several HCV treatment centers have found disappointingly low follow-up among IDUs and/or coinfecting patients who are referred off-site for care [196;219;220;248]. Further, building upon, or integrating into, existing infrastructure makes the most of limited resources.

While there are few programs for care of HIV/HCV-coinfecting IDUs, there are several geared toward HCV-monoinfecting IDUs. Together these programs may serve as templates for providers seeking to establish their own centers of care. The following is a list of some of the programs published in the literature:

► **Brown Medical School’s Miriam Hospital Immunology Center, Providence, Rhode Island**

In 2001, an HCV clinic was integrated into a pre-existing primary care center for persons living with HIV [246]. HCV education and coinfection support groups are offered on-site. An on-site psychiatrist and social workers and use of buprenorphine, along with collaboration with community-based mental health and drug treatment centers, allows the center to provide integrated psychiatric care, addiction treatment, case management, and counseling. Communication with HIV/primary care physicians, a consulting hepatologist, AIDS service organizations, drug treatment centers, mental health providers, and correctional re-entry programs permits individualized care. Patients with active substance use including IDU may receive HCV treatment, which is administered along with risk reduction education. The cornerstone of the program is supervised therapy; patients come to the clinic each week for coordinated IFN injections, side effect management, phlebotomy as needed, and support group services. Thus far, the center has achieved high rates of follow-up for evaluation of HCV-related liver disease (55 percent) and adherence to weekly IFN visits (exceeding 90 percent) [249].

► **Organization to Achieve Solutions in Substance Abuse (OASIS), Inc., Oakland, California**

Diana Sylvestre was one of the first physicians to establish an HCV treatment and research center geared toward IDUs and individuals on methadone [245]. OASIS provides comprehensive medical, mental health, and vocational services to underserved members of the community with HCV, HIV, and addiction. Support and information sessions are held weekly at the clinic, with synchronized phlebotomy and medical appointments. In a study conducted before availability of peg-IFN,

76 patients on methadone maintenance were treated with IFN/RBV. Patients were eligible for treatment if they attend at least 75 percent of these weekly groups for a period of two months or more, regardless of concurrent drug use. Subjects with untreated depression were considered for treatment after they were stabilized with psychotropic medications; ultimately, 59 percent of patients enrolled had a previous psychiatric diagnosis. The overall SVR was 28 percent. SVRs appeared to be lower among those with occasional drug use than among those with no drug use, and SVR among those with regular drug use was lower still. However, these differences were not statistically significant. Studies investigating ways to transition active, street-recruited heroin users to HCV treatment are ongoing. Sylvestre is investigating the impact of integrating treatment for active heroin use with buprenorphine into HCV treatment, versus the usual care model of offering drug treatment as a separate modality.

► **Tarbes Hospital Hepato-gastroenterology Unit, Tarbes, France**

This medical center established a “dual management objective” over 10 years ago which integrated care for HCV and drug addiction [62]. Many services are provided on-site by physicians, nurses, social workers, and psychologists, including HCV care and methadone maintenance. The authors looked back at the 435 patients treated between 1990 and 2000, and divided them into 4 groups: active IDUs not on substitution therapy; active IDUs on substitution therapy; former IDUs; and non-IDUs. They found that there was no difference between the groups with regards to adherence or SVR. Overall SVR was 22 percent.

► **Detoxification Unit, Munich-Schwabing Hospital, Munchen, Germany**

An HCV treatment program was integrated into this detoxification center based at a general hospital [243]. Fifty drug dependent patients were treated with the support of specialists in both hepatology and addiction medicine. They were started on IFN/RBV (the study was conducted before the availability of peg-IFN) before leaving the detoxification program, and continued the treatment upon discharge, with weekly visits by the specialists. Patients who relapsed were offered opiate replacement, but were not discontinued from HCV treatment. Thirty-six percent of patients achieved an SVR. Only 10 percent discontinued due to noncompliance; 39 patients missed no interferon injections up until the end of treatment, regardless of why treatment was terminated. Overall, 80 percent of patients had at least one relapse, 30 percent of which were admitted to a methadone maintenance program. None were reinfected. There was no statistical difference between SVR in patients who were abstinent versus patients who relapsed.

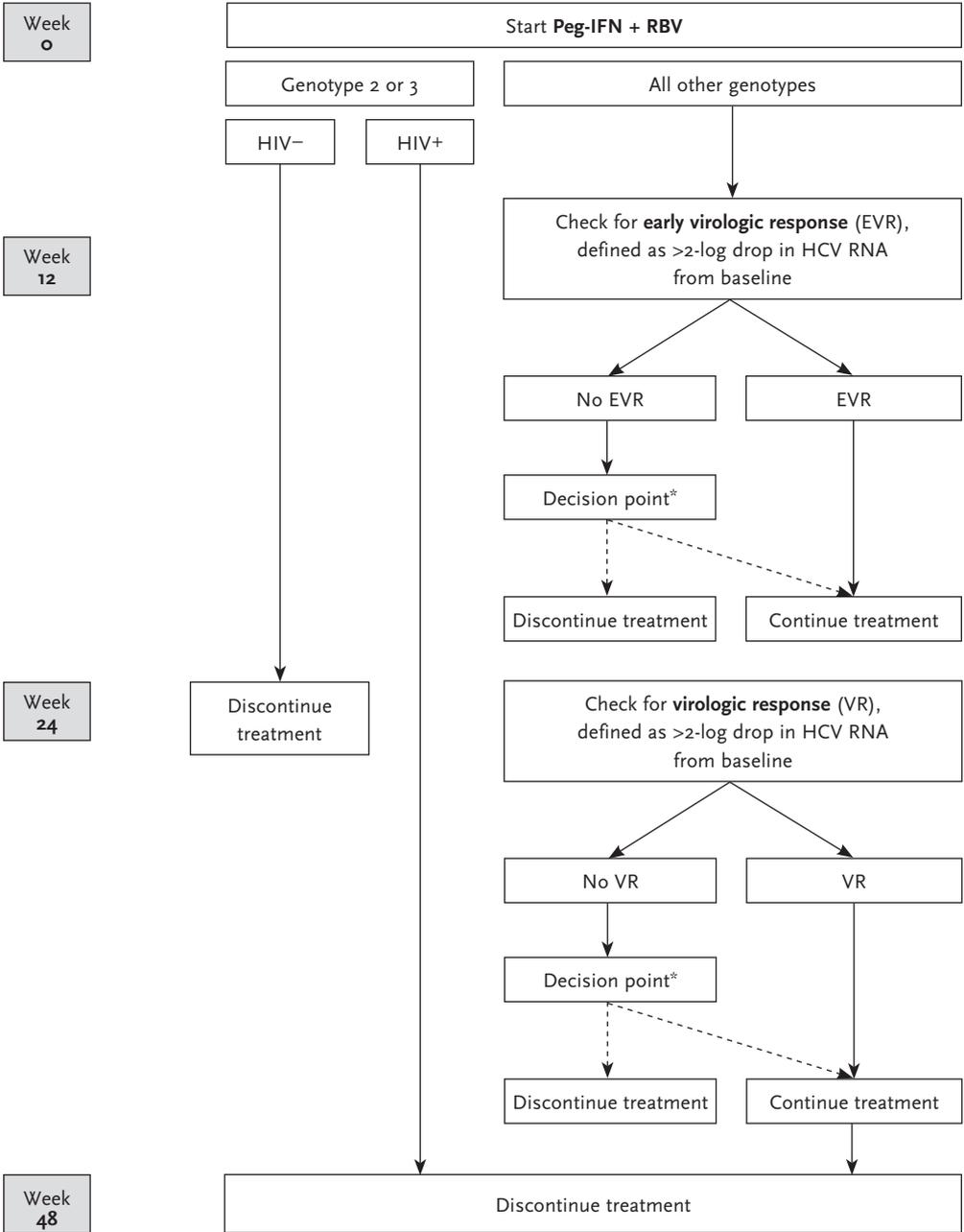
## Conclusions

Given the large numbers of coinfecting IDUs worldwide, the question of whether to address HCV in HIV-coinfecting IDUs is moot. The more apt question is how to do so most effectively. Access to HIV care and medications, and reducing barriers to HIV treatment entry for drug users, remain the most vital issues for the bulk of the world's coinfecting IDUs. Access to HCV medications will become a larger concern as generic HIV antiretrovirals become more widespread in the developing world. With treatments for both viruses in place, the optimal time sequence of HIV and HCV treatments will become an important consideration.

**Table 1.** Global HCV Prevalence among HIV-positive persons

<i>Location</i>	<i>Cohort</i>	<i>Prevalence</i>
Santos, Brazil [17]	HIV+ cross-section, including IDUs	36%
Alberta, Canada [15]	Local HIV+ cross-section, 91% IDU	61%
Sichuan Province, China [19]	Drug users	100%
London, England [14]	Ethnically diverse HIV clinic population	9%
Nigeria [16]	HIV+ with access to ART	8%
San Juan, Puerto Rico [18]	Population-based	92%
Thailand [20;21]	Cross-section of HIV clinic population; young HIV+ men	8–50%
United States [12;13]	Variety of HIV+ cohorts	16–45%

**Figure 1.** HCV treatment algorithm



\*Chance of SVR at this point is exceedingly low, so the goal of treatment, if continued, is delaying histologic and clinical disease progression. Hepatitis C disease stage, treatment tolerability, and individual factors should be considered when deciding whether to discontinue.



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The significant individual and community burden imposed by both TB and HIV requires effective, accessible and acceptable TB and HIV prevention and care for IDUs.

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# HIV and Tuberculosis Coinfection

Philipp du Cros and Adeeba Kamarulzaman\*

## Introduction

The confluence of the two epidemics of HIV and tuberculosis (TB) presents one of the greatest threats to public health today. Effective treatment is available for both conditions [1] but concurrent treatment of HIV and TB coinfection presents major challenges to both the person living with HIV/AIDS (PLWHA) and the care provider. Injecting drug users (IDUs) have an increased risk of both conditions [2;3], but have often suffered from decreased access to and utilization of health services [4;5], and antiretroviral therapy in particular [6]. Decreased adherence to treatment amongst IDUs managed in traditional settings with anti-TB medications and antiretrovirals (ARV) is a significant problem [7]. The significant individual and community burden imposed by both TB and HIV requires effective, accessible and acceptable TB and HIV prevention and care for IDUs.

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# Global Prevalence of HIV / Tuberculosis Coinfection

Approximately 2 billion people, or one third of the world's population, are infected with the tuberculous bacilli. The World Health Organization (WHO) estimated that there were 8.9 million new cases of TB in 2004, of which 741,000 were also infected with HIV. In that year an estimated 2 million people died from TB, of which 248,000 were coinfecting with HIV [8]. The burden of HIV and TB coinfection varies widely by region, ranging from 60 percent in East and Southern Africa to 3.3 percent in the United Kingdom and 15 percent in Spain. The largest numbers of co-infected adults were in South Africa (2.0 million), India (1.7 million), and Nigeria (0.9 million) [9]. The impact of HIV on the incidence of TB has been marked even in countries with previously low prevalence of TB. In the United States, it was estimated that 26 percent of active TB cases were attributable to HIV [9]. In other countries where the incidence of TB had been declining, a resurgence of the disease was seen in recent years concurrent with an increase in the HIV epidemic. The rapid rise in HIV and TB is especially concerning in countries of the former Soviet Union where explosive HIV epidemics were noted, particularly amongst IDUs [10–13]. In Ukraine, the incidence of active TB doubled between 1992 and 2002 after several years of decline [13].

Of the six WHO regions, the Asian region has the highest burden of TB in the world. In recent years it has also experienced an alarming acceleration in the HIV epidemic, including in countries with a high burden of TB such as China, Indonesia, Vietnam, and Cambodia. In many of these countries, injecting drug use has been the main mode of spread of the HIV epidemic [9;14]. Recent reports from the region have recorded HIV prevalence in TB patients of 12 percent in Cambodia and Thailand, 11 percent in Myanmar, and 4 percent in Vietnam [15]. Although the rates of HIV and TB coinfection in Asian countries are lower in comparison to African countries, the absolute number of coinfecting persons already exceeds 2 million [9].

Large variations exist between the countries in each region, and between different locations, ethnic groups, and HIV risk groups within each country. In India, the reported prevalence of HIV amongst patients with active TB has varied between 0.4 percent and 28.8 percent in different cohorts [16]. In the United States, HIV and TB coinfection rates have been highest in four areas of the country, with Florida, New York City, Texas, and California accounting for 53 percent of all reported HIV and TB coinfection in the country [17].

## Prevalence of HIV/Tuberculosis Coinfection among IDU Populations

Low socioeconomic status, homelessness, poor nutrition, overcrowding, poor environmental conditions, and problems of access to primary health care are associated with both drug use and TB. Hence, drug use was a major risk factor for TB even before the emergence of the HIV epidemic [18;19]. Furthermore, injecting drug use has been shown to be an independent risk factor for the progression of latent TB to active disease, although the mechanism has not yet been defined [20;21].

The association between HIV/TB co-infection and injecting drug use was recognized early in the AIDS epidemic. In a review at a New York City hospital between 1978 and 1985, active TB occurred in 15.1 percent of AIDS patients with a history of IDU and 4.4 percent of all other patients with AIDS. The yearly rate of TB more than doubled during the study period, which was entirely attributable to cases among IDU patients with AIDS [22]. In Catalonia, Spain, the annual active TB crude incidence rate increased by 50 percent between 1987 and 1993, with at least 60 percent of the increase directly related to AIDS. Multivariate analysis from those AIDS cases showed the strongest predictors of TB among AIDS cases were history of imprisonment (odds ratio, 2.16;  $P < 0.001$ ) and injecting drug use (odds ratio, 1.65;  $P < 0.001$ ) [23]. More recently in a series from St. Petersburg, Russia, 94 percent of HIV-infected culture positive TB cases were individuals with a history of injecting drug use [11]. The role of a positive HIV status and injecting drug use in the spread of TB was examined in a case-control study of smear-positive pulmonary TB patients in Spain. In this study, HIV-seropositive index cases were observed to cause more TB microepidemics than HIV-seronegative cases. All index cases in these microepidemics were HIV-seropositive IDUs [24].

## Effect of TB on HIV Disease Progression

Several studies have demonstrated an increased risk for progression of HIV disease and poorer outcomes in patients coinfecting with TB [25]. Production of pro-inflammatory cytokines by TB lesions has been associated with increased HIV viraemia in vitro, and is hypothesized to accelerate immunosuppression in HIV [26;27]. Other reasons that coinfection with TB worsens the prognosis of HIV include delays in diagnosis as a result of atypical presentation, and poorer absorption of treatment [27]).

## Impact of HIV on TB

HIV-positive IDUs are at much higher risk for progression from latent infection to active TB compared to HIV-negative IDUs and the general population [3;28]. In a cohort of drug users in Amsterdam, Keizer and colleagues demonstrated that the incidence of latent TB in HIV-negative IDUs is six times higher than in the overall Amsterdam population, while HIV infection increases the risk for active TB in these IDUs by thirteenfold [29]. Incidence rates of active TB are especially high in HIV-infected IDUs with a positive tuberculin skin test result, with rates ranging from 4.6–18.8/1000 person-years [2;30]. It has recently been shown that the risk for conversion from latent to active TB appears to be in the early (years 4–6) and later stages (after year 9) of HIV infection [2;30].

## HIV/TB Coinfection in Prisons

Factors that fuel HIV and TB coinfection amongst IDUs are further amplified in correctional settings. Overcrowding, poor physical conditions including poor ventilation, and lack of adequate treatment result in significant rates of TB in prisons around the world. In many of these institutions, TB is a major cause of death amongst prison inmates (31). High prevalence of HIV and TB coinfection in correctional settings has been reported in many countries, including 35 percent in southern Thailand, 26 percent in Tanzania, 20 percent in Spain, 12 percent in Russia, and 11.7 percent in Malaysia [32–36].

In many countries, a significant proportion of incarcerations are for drug-related offences and incarceration is also a common experience for many IDUs [37]. Correctional settings present a particular challenge for control of TB transmission. Several outbreaks of TB amongst inmates with HIV infection in correctional settings have been described [38–40]. In a longitudinal study of transmission of TB in a large prison population, 26 percent of isolates showed a unique fingerprint, with evidence of recent infection occurring in approximately 62 percent of these patients. Eighty-four percent of patients tested were HIV-positive [41]. In addition to transmission within the prison setting, transmission from prison inmates into the general population has been described. A restriction fragment length polymorphism analysis on culture-positive cases of TB in Madrid showed the dissemination of common strains of *Mycobacterium tuberculosis* between prison inmates and the urban population of Madrid. Risk factors associated with the dissemination of common strains of TB amongst prison inmates and the urban population of Madrid included HIV infection, intravenous drug use, and current or previous imprisonment [42].

Prison populations have higher rates of multidrug resistant (MDR) TB in comparison to the general population [43–45]. In the early 1990s, three epidemiologically linked MDR-TB outbreaks involving New York State prisons were described [46;47]. The potential for transmission of MDR strains of TB within the prison setting, and from prisons into the community, is of real concern.

## Clinical Presentation

Active TB in HIV-infected patients most commonly presents with pulmonary involvement [48–51]. In patients with relatively preserved CD4 counts, presentation is similar to HIV-uninfected adults with upper lobe involvement, cavitation, and positive sputum smear [52–55]. In contrast, patients with more profound immunosuppression (CD4 < 200 cells/mm<sup>3</sup>) usually present with a primary TB pattern; tuberculous pneumonia, often with lower lobe involvement, mediastinal or hilar lymphadenopathy, and miliary involvement are common, while cavitation is seen uncommonly [52–54;56–58]. Sputum smear is more often negative in immunosuppressed patients [59–61], potentially delaying diagnosis. However, sputum smears may be positive in the presence of a normal chest radiograph in approximately 5 percent of patients with pulmonary TB and HIV [54].

Extrapulmonary TB is more common in HIV-infected than noninfected patients [62;63], becoming increasingly common with progressive immunodeficiency [64]. While all forms of extrapulmonary TB have been described in HIV and TB coinfecting patients, the commonest presentation is lymphadenopathy [65;66]. Other common presentations include pleural effusion, disseminated TB, and TB meningitis [1;67]. Abdominal TB often presents with organ involvement and lymphadenopathy in the setting of disseminated TB [68]. In some cases, the only symptom of TB may be unexplained persistent fever [69].

When assessing for TB in an HIV-positive patient, it is important to consider differential diagnoses, including opportunistic infections which may resemble TB in HIV-infected persons (1). *Pneumocystis jirovecii* (formerly *Pneumocystis carinii*) is an important differential diagnosis especially in smear negative patients. In addition, profoundly immunosuppressed patients may present with more than one infection. Dual infection with *M. tuberculosis* and *Pneumocystis jirovecii* or with *M. tuberculosis* and streptococcal pneumonia have been reported [70–72].

## Diagnosis of Active Tuberculosis

Due to the difficulty of distinguishing TB from other diagnoses on clinical grounds with high reliability, it is important to seek confirmation of the diagnosis, where possible, in all suspected patients. Confirmation of the diagnosis decreases the frequency of prolonged anti-TB treatment in uninfected patients. Sputum microscopy remains the quickest method of helping establish a diagnosis of pulmonary TB. Recent guidelines by the International Standards for Tuberculosis Care propose that all patients suspected of having pulmonary TB should have at least two, and preferably three, sputum specimens obtained for microscopic examination. When possible, at least one early morning specimen should be obtained [73]. Mycobacterial cultures remain the gold standard for both diagnosis of TB and drug sensitivity testing. However, for many countries in the world, cost and access to adequate laboratories limit the use of such testing. In addition, several weeks are required for a culture result, limiting usefulness in initial treatment decisions. Consequently, in resource limited settings, current WHO guidelines recommend diagnostic algorithms that do not include mycobacterial cultures [1].

HIV-infected patients with smear negative TB have higher fatality rates than those with smear positive TB [9], with resulting delays in treatment likely to be one major reason for this [63]. Clinical algorithms to improve the diagnosis of smear negative pulmonary TB in HIV-infected patients are being revised, but require further research to demonstrate improvements in diagnosis and outcomes [74].

Currently, the role of direct amplification tests for the diagnosis of TB in HIV-infected patients is not clear [75]. The cost and required laboratory expertise ensure that they are not currently useful in resource-limited settings. They have been recommended for distinguishing *M. tuberculosis* from nontuberculous mycobacteria in smear positive respiratory samples [76]. Small studies have advocated a role for these tests in helping establish an early diagnosis in HIV patients with smear negative TB [75;77], however sensitivity and specificity are low, requiring that cultures still be performed [78].

Sputum induction with hypertonic saline is useful in suspected pulmonary TB patients who are unable to produce sputum [1], with a reported diagnostic yield similar to that of bronchoscopy [79]. The diagnostic yield from induced sputum can be improved by repeated specimens [80]. Sputum induction culture has a high yield in the diagnosis of tuberculous pleural effusion, even in the setting of normal lung parenchyma on chest X-ray [81]. However, sputum induction results in an increase in droplet spread and should be performed with appropriate precautions by trained personnel to minimize the risk of spread to other patients and to health care workers [1]. While recovery of *M. tuberculosis* from blood cultures is uncommon in HIV-seronegative patients, it is common in extrapulmonary TB in HIV-infected patients [82]. The prevalence of positive blood cultures increases with a decline in CD4 count. One study reported that 29

percent of 75 HIV-infected patients presenting with TB were mycobacteremic, including 49 percent of those with a CD4 count less than 100 cells/ $\mu$ L [64]. When less invasive tests have not provided a diagnosis and the patient's clinical condition argues against waiting for culture results, then invasive testing should be considered, including bronchoscopy, bone marrow biopsy or lymph node biopsy [76].

The tuberculin skin test (TST) has little value in the diagnosis of active TB in HIV-infected patients [83]. A positive TST does not distinguish active from latent infection, and previous exposure to environmental mycobacteria or BCG vaccination may also result in false positive results [84]. The TST is often falsely negative in the presence of HIV infection especially in those with advanced immunosuppression, and may also be falsely negative due to severe malnutrition or miliary TB [85].

## Treatment

The standard six month short course treatment regimen has shown similar results for susceptible *M. tuberculosis* in HIV-infected compared to HIV-uninfected patients [86–89]. Improvement in clinical condition occurs at a similar rate between HIV-infected and uninfected patients treated for TB, except that weight gain may be slower in HIV-infected patients [1;90]. Time to sterilization of sputum and radiological improvements are also similar [1;91;92]. The standard six month regimen results in similar rates of treatment failure for HIV-infected persons as for HIV-uninfected persons [86–89].

TB recurrences are more likely in patients with CD4 below 100 cells/ $\text{mm}^3$  especially in areas of high endemicity [93], and mortality rates with recurrence are high [89;93]. Two trials have reported lower rates of relapse with nine to twelve months of treatment compared with six month regimens in HIV-infected patients [94;95]. Due to limitations in the studies, it is unclear whether this reflects a true superiority of longer duration treatment or a reduction in exogenous reinfection rates [96].

Current recommendations for TB treatment in HIV-infected persons are for six months treatment with a rifampicin based regimen consisting of two months for the initial phase and four months for the continuation phase (see Table 1). However, six months is the minimum treatment duration; extending treatment to nine months with a seven month continuation phase is recommended for those with a slow clinical or microbiological response (e.g. cultures remain positive at two months) [1;76; 78]. Extrapulmonary TB should be treated for the same duration as pulmonary TB, except for TB meningitis which should be treated for twelve months. The addition of corticosteroids should be considered for patients with tuberculous pericarditis and meningitis [76;78].

An alternative treatment regimen consists of changing the continuation phase to isoniazid and ethambutol for six months. If problems with adherence are anticipated, then this regimen minimizes the risk of development of rifampicin resistance. However, this regimen is associated with higher rates of failure and relapse, especially amongst HIV-infected patients [73].

Treatment for susceptible *M. tuberculosis* can be administered as daily or intermittent therapy. Twice weekly regimens have been associated with increased risk of rifamycin resistance in patients with low CD4 counts, and consequently are not recommended in current WHO guidelines [115;73]. The use of fixed dose regimens may be particularly helpful in the treatment of IDUs as they reduce the number of tablets per day and the risk of inadvertent monotherapy. Once weekly regimens (e.g. rifapentine-isoniazid) should not be used in HIV-infected persons because of high rates of failure with rifamycin resistant TB [97]. Where rifabutin is available, many physicians prefer to substitute this in place of rifampicin.

At present the optimal treatment for drug resistant TB remains controversial. When initiating or revising treatment, it should ideally consist of at least three previously unused drugs to which there is susceptibility [98]. A single drug should never be added to a failing TB regimen [1]. Patients should be hospitalized or treated with directly observed therapy; intermittent therapy should be avoided [98]. Suggested regimens are listed in Table 1.

Simultaneous treatment of TB and HIV is fraught with difficulties. The increased number of medications results in an increased risk of drug interactions, toxicities, and poor adherence to treatment. These factors can potentially result in microbiological and/or virological treatment failure. However, delays in instituting highly active anti-retroviral therapy (HAART) in immunosuppressed HIV patients are associated with an increased risk of opportunistic infection and mortality [76;99].

## Overlapping Toxicity Profiles for Tuberculosis and HIV Treatment

High rates of side effects have been reported in HIV and TB-coinfected persons commencing TB treatment, with rates of intolerance of TB treatment requiring change reported between 6 and 18 percent prior to the HAART era [100;101]. In patients receiving combined TB treatment and ARVs, adverse events as high as 54 percent have been reported [99]. The most common adverse events are peripheral neuropathy, rash, and gastrointestinal upset. The majority of adverse events occur within the first two months, and commonly necessitate interruption of TB or HIV therapy [99]. Patients with lower

CD4 counts may be at higher risk of intolerance to rifampicin [102]. Rates of peripheral neuropathy and parasthesia are high, suggesting that all HIV-infected patients should receive pyridoxine when being treated for TB [76]. The large number of medications necessary for concurrent treatment of both TB and HIV greatly increases chances of toxicity. Common side effects encountered are listed in Table 2.

Hepatotoxicity during TB treatment is increased in HIV-infected patients. Minor increases in liver aminotransferases are common during TB treatment, however significant hepatotoxicity should be considered as a serum AST or ALT more than three times the upper limit of normal, together with symptoms, or AST or ALT more than five times the upper limit of normal [78]. Risk factors for hepatotoxicity include increasing age, heavy alcohol use, female sex, and hepatitis B and hepatitis C infection [78;103–105]. Rates of hepatotoxicity in patients coinfecting with HIV and hepatitis C treated with anti-TB medications were increased fourteenfold in one study [106], which is of particular concern when treating IDUs. If hepatotoxicity occurs then all potentially hepatotoxic drugs should be ceased including isoniazid, rifampicin, and pyrazinamide, as well as medications such as ARVs and cotrimoxazole. First line agents can usually be reintroduced gradually with increasing dosage over a period of two weeks once serum AST or ALT decreases to less than two times the upper limit of normal [78]. Recovery of liver function may be slow, and depending on the patient's clinical condition, a temporary TB regimen that is unlikely to cause further hepatotoxicity may need to be introduced until first line agents recommence.

Lower serum concentrations of anti-TB agents, most notably rifampicin and ethambutol, have been reported in HIV-infected patients [107;108]. Lower absorption due to HIV enteropathy or opportunistic infection involving the digestive tract may result in subtherapeutic serum drug levels and has been associated with treatment failure [109;110]. Some authors have suggested that therapeutic drug monitoring of anti-TB agents may be helpful [111;112], however there is limited access to these facilities and currently a lack of evidence of improved outcome in this setting.

## Drug-Drug Interaction Between Tuberculosis Treatment and Antiretrovirals

Rifampicin is a strong inducer of the cytochrome P<sub>450</sub>-3A<sub>4</sub> (CYP-3A<sub>4</sub>) drug metabolizing system. Induction of CYP-3A<sub>4</sub> hastens drug metabolism, which can result in sub-therapeutic levels of coadministered protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs) [113;114]. Pharmacokinetic interactions between rifampicin and some NRTIs also occur through mechanisms other than induction of CYP-3A<sub>4</sub>, most

notably a reduction in serum levels of zidovudine. However, these have not been shown to have clinical relevance and dose adjustment is not recommended [112;115].

Rifamycins can all induce CYP-3A4, although with differing potency: rifampicin is the most potent, followed by rifapentine, and then rifabutin as the least potent (116). Consequently, rifabutin provides greater options for combined treatment with HAART as it can be safely used with most protease inhibitors and NNRTIs [115].

Rifamycins may interact with a wide range of other medications commonly used in HIV-infected persons. Rifampicin may result in lower serum concentrations of dapsone, glucocorticoids, and fluconazole [112]. Ideally, use of itraconazole and rifampicin should be avoided, but if concomitant treatment is required then the itraconazole dose needs to be increased with close clinical monitoring [112]. Combining rifabutin and clarithromycin has an increased incidence of uveitis [117;118].

Rifampicin enhances methadone metabolism resulting in a 33 to 68 percent decrease in plasma methadone concentrations such that an increase in methadone dose is required [119]. Rifabutin has not been shown to significantly alter methadone levels [120]. Buprenorphine is also mainly metabolized by CYP-3A4, and thus rifampicin may result in lowered levels of buprenorphine [121]. Naltrexone is not known to have significant interactions with first line TB medications. To the best of our knowledge, there are no studies evaluating interactions between anti-TB medications and illegal drugs.

Other first line TB agents may also have interactions with ARVs, although this is thought to be less of a problem than rifampicin. Isoniazid has recently been shown in vitro to be an inhibitor of cytochrome P450 [122], which could potentially cause interactions with ARVs. Whether this has any clinical significance is not yet known, and current guidelines do not recommend any dose adjustments of isoniazid or ARVs when concurrently administered [76;78].

## Choice of HAART Regimen

The extensive interactions between rifampicin and ARVs greatly limit the available options for coadministration (Table 3). In addition, the optimal choice of HAART regimen requires consideration of medication availability and cost, national tuberculosis and HIV treatment plans, and patient factors. For example, although rifabutin is discussed as an option for TB treatment in place of rifampicin, the reality in most resource-limited settings is that this medication is not available or it is too expensive.

Most experience in treating HIV and TB coinfection has been with rifampicin and efavirenz coadministration, although controversy still remains about the optimal dosing of efavirenz [78]. It has been suggested that the dose of efavirenz should be increased to 800 mg daily in those weighing greater than 60 kg in order to reduce the risk of sub-

therapeutic levels of efavirenz and subsequent resistance development [123]. However this may result in an increased risk of efavirenz toxicity, most notably neuropsychiatric side effects [124]. An open label randomized study in Thailand showed similar virological and immunological outcomes at 48 weeks comparing 600 mg with 800 mg dosing of efavirenz, suggesting that dose adjustment of efavirenz is not required [125].

Treatment choice becomes more difficult in situations where efavirenz is not appropriate, such as with efavirenz-associated intolerance, NNRTI resistance, or with women who are pregnant or without access to effective birth control. Currently, evidence of the safety and effectiveness of combined rifampicin and nevirapine is limited [126–128]. Interactions with reduced nevirapine levels have been observed and there is an increased risk of hepatotoxicity. However, similar response rates without dose adjustment of nevirapine have been reported. On present evidence, this combination should be a second line option and the patient should be closely monitored [76;129]. There is limited experience with the two recommended ritonavir boosted protease inhibitor regimens, and there is significant concern about increased hepatotoxicity [130].

Rifabutin substituted for rifampicin has been successfully used for TB treatment [131]. Rifabutin has less significant interactions with many ARVs making it an attractive option for HIV and TB-coinfected patients (Table 4). However, despite frequent use of rifabutin-based regimens, there are no large scale trials providing evidence of their efficacy in HIV-infected patients. In resource limited settings, rifabutin-based regimens are not feasible due to high cost and lack of availability. Similar to problems with intermittent rifampicin regimens, twice weekly rifabutin has been associated with a 5 percent rate of failure or relapse with rifamycin resistant *M. tuberculosis* in patients with CD4 counts less than 100 cells/mm<sup>3</sup> [132].

Avoidance of rifamycins in TB treatment is theoretically an attractive option for reducing potential interactions between anti-TB medications and HAART. However, nonrifamycin-based regimens require increased duration and are inferior to rifampicin-based regimens for treatment of TB in HIV-infected patients [9;133]. Treatment regimens that use a rifampicin-based initial phase followed by an isoniazid and ethambutol continuation phase have higher failure rates than standard short course treatment [134]. It has been suggested that the antibacterial effect of rifampicin may be beneficial in addition to its anti-TB effects in patients with advanced HIV, providing treatment or prevention of bacterial coinfections [1]. Nonrifamycin-based regimens should generally be limited to the setting of rifamycin-resistant *M. tuberculosis*, or patients with serious toxicity to rifamycins where reintroduction has failed [78].

Patients requiring combined TB and HIV treatment can also be treated with triple NRTI/nucleotide RTI regimens, thereby decreasing many of the problems associated with interactions [76;135]. Single tablet formulation of NRTIs (zidovudine, lamivudine, and abacavir) is attractive for treating IDUs, as the lower pill burden may aid adher-

ence. However, evidence suggests that triple NRTIs are less effective HAART regimens [136–138] and should be used only when other options are not appropriate and when close monitoring is possible.

## When to Commence HAART

The decision about when to commence HAART is a balance between the need to simplify treatment versus the risk of disease progression. Delaying commencement of HAART simplifies management with fewer side effects and drug interactions, and less risk of paradoxical reactions. Early initiation of HAART during TB treatment is associated with a high incidence of side effects [99]. In addition, the introduction of a large number of medications at once is a significant adherence challenge, which is often an important concern when treating IDUs. However, treatment with TB therapy alone does not lead to significant increases in CD4 counts or reduction in HIV viral loads [139;140]. Mortality due to progression of HIV and occurrence of opportunistic infections during TB treatment is high in those with advanced immunosuppression, especially during the two month initial phase of anti-TB treatment [27;141].

Currently, the optimal timing of commencing HAART in patients coinfecting with HIV and TB remains unknown. A pragmatic approach is outlined in Table 5. In patients with CD4 counts less than 200 cells/mm<sup>3</sup>, HAART should be commenced early, however delaying commencement until two to eight weeks after starting TB treatment helps with identifying causes of toxicity. Regular clinical and laboratory monitoring should be conducted in patients where HAART is being delayed. Despite this guide, the exact timing should be individualized, taking into account not only initial response to TB treatment and occurrence of side effects, but also other factors that may be extremely important in improving adherence amongst IDUs, including drug substitution treatment, case management, and attention to social issues [7;142].

## Patient Provider Partnership

Adherence to treatment is the most important factor in determining treatment outcomes. Poor adherence to TB medication may result in prolonged infectiousness, drug resistance, relapse of TB, and increased mortality, and therefore has consequences both for the individual and the community [1]. An estimated 20–50 percent of patients will not complete TB treatment within a 24-month period [143]. While active drug and alco-

hol use are predictors of poor adherence, a past history of substance abuse or current stable enrolment in a drug treatment service are not [7;144–146]. Traditional health care models have often been inappropriate for IDUs needs and quick to label IDUs as “non-compliant.” A patient centered approach requires consideration of patient’s needs as well as patient, social, and service provider factors that may aid adherence to drug treatment. Treatment often needs to be tailored to individual patient requirements rather than applying a generic “one system fits all” approach.

Current WHO guidelines recommend that treatment support measures, which may include directly observed therapy (DOT), should be individualized to suit the patient [73]. DOT, as part of a comprehensive treatment program, is associated with improvements in treatment completion rates and outcomes, a decrease in incidence of TB in the community and reductions in drug-resistant TB [147–150]. However, debate still remains regarding whether DOT is more effective than self administered treatment [151]. Several studies in low income settings have not shown a benefit of DOT over self-administered treatment [152–154]. Reported benefits of DOT programs may relate to additional program factors other than just simply observing treatment. Other strategies commonly used in DOT programs include tracing of defaulters, staff motivation, and patient centered approaches including education and incentives [151;155]. DOT, either facility based or community based, may help in early identification and appropriate intervention for adverse events.

Several approaches have been reported to improve adherence in IDUs including flexible clinic hours, accessible medical staff, and cash or food incentives [7;145;156;157]. A multidisciplinary approach for IDUs must consider social service support, housing assistance, treatment for substance misuse, and coordination of TB services with other service providers [142]. Substance abuse treatment programs and needle exchange programs administering DOT have reported good rates of adherence to TB treatment and to HAART [145;158;159].

## Paradoxical Reactions and Immune Reconstitution Disease

Patients who receive effective treatment for TB and initially respond well, may suffer from “paradoxical reactions” consisting of clinical or radiological deterioration of pre-existing tuberculous lesions or the development of new lesions [160]. Paradoxical reactions have been reported in 2–23 percent of HIV-seronegative patients commencing TB treatment [161;162]. Paradoxical reactions are more common in patients commenced

on HAART [160]. Lower rates have been reported when there is a delay between commencing TB medications and HIV medications [99]. It seems likely that paradoxical reactions in coinfecting patients are, at least in part, a form of HAART related immune reconstitution disease (IRD) [163].

Paradoxical reactions often present with swinging fevers, rapidly enlarging lymphadenopathy, worsening pulmonary infiltrates, and an increase in pre-existing TB lesions [163–165]. A diagnosis of paradoxical reactions should only be made after consideration and investigation of other potential causes including other opportunistic infections, drug reactions, poor adherence, poor absorption of TB medications, and drug resistant TB. Diagnosis may be difficult as there is no diagnostic test. Supporting evidence for the diagnosis of paradoxical reactions may include a substantial increase in TST result [160], and a rapid rise in CD4 count [163;166].

Paradoxical reaction is uncommonly the first presentation of TB [163]. The majority of cases occur in patients commencing HAART within three months of commencing TB treatment [166], with one review reporting onset at a median of eight weeks after commencing a TB regimen and four weeks after commencing HAART [163]. Patients who develop paradoxical reactions are more likely to have a CD4 count less than 100 cells/mm<sup>3</sup> prior to commencement of HAART, HIV viral load > 10<sup>5</sup> copies per ml, presentation with disseminated TB and a rapid response to HAART [162;163;165;166]. In a recent study, 70 TB smear positive HIV-infected patients in Tanzania were randomized to receive Trizivir (zidovudine, lamivudine, abacavir single formulation) either within 14 days of commencing TB treatment or delayed for two months [129]. Treatment was well tolerated, and there were no cases of TB-associated IRD observed in either group. CD4 count increased by a median of 113 cells/mm<sup>3</sup>, lower than would be expected with efavirenz-based HAART, raising the possibility that occurrence of paradoxical reactions relates to the rate of rise of the CD4 count [129].

Paradoxical reactions are generally self limited [160]. If not severe, symptomatic treatment is usually sufficient without changing HIV or TB therapy [76]. Evidence for the best management of severe reactions is lacking, but current guidelines recommend glucocorticoid treatment [78]. HAART may need to be temporarily discontinued but this should be done with caution as it can lead to rapid declines in CD4 count [78;163]. It is important to consider potential interactions between rifampicin and prednisolone, with treatment often requiring commencing prednisolone or methylprednisolone at 1–2 mg/kg and gradually reducing after one or two weeks [76, 163]. The exact dose and duration should be tailored to the individual case.

## Prevention of Tuberculosis

Isoniazid preventive therapy (IPT) in HIV-infected patients has been shown to have a protective effect, although the effects were greater amongst those with a positive TST result compared with those with a negative TST result [84]. Reviews of randomised controlled trials suggest that IPT results in a risk reduction of over 40 percent in the rate of active TB in HIV-infected patients. However, the protective effect is short lived, only lasting two to four years, and whether IPT reduces mortality is not certain [167]. Currently isoniazid treatment is recommended for six to nine months, with the suggestion that nine months is more effective than six months [1;76;156]. The small benefit of longer duration IPT needs to be weighed against risks of adherence to an extra three months of medication when treating IDUs. Short courses of chemoprophylaxis with rifampicin and pyrazinamide for two months are equally effective, but have been associated with increased rates of fatal hepatic reactions and are currently not recommended [115]. Chemoprophylaxis with greater than six months of isoniazid has been shown to significantly reduce rates of active TB in HIV-infected IDUs with positive TSTs attending methadone treatment programs. However, rates of contraindications to chemoprophylaxis, refusal of treatment, and non-adherence were high in this study [168]. Isoniazid treatment of latent TB in IDUs infected with hepatitis C has not been associated with an increase in hepatotoxicity [169;170], although it seems prudent to monitor liver function tests monthly.

All HIV-infected patients, and especially IDUs who are at high risk of TB, should have a TST for assessment of latent TB infection [3;76]. Use of monetary incentives in the setting of a needle syringe exchange program has been shown to be highly effective in increasing adherence to screening for latent TB among IDUs [156;157]. It is important to exclude active TB prior to instituting chemoprophylaxis. Patients should have a clinical assessment, chest X-ray and, when indicated, sputum smear and culture to exclude active TB [1]. IPT should be offered to HIV-infected persons with induration greater than or equal to 5 mm or recent close contact with a confirmed case of active TB [76]. Secondary chemoprophylaxis post-treatment in areas of high endemicity can reduce the risk of TB recurrence (171) but has not been shown to improve survival rates.

Recently, peripheral blood T-cell based interferon assays have been developed and have shown promising results when compared with TST in diagnosing latent TB infection. However, there is currently not enough evidence of performance in patients with HIV infection to advocate for their use [172].

HIV-infected persons and staff are at risk of TB infection in health care settings, most notably in infectious disease and TB wards. Sunlight kills *M. tuberculosis*, and good ventilation decreases the risk of transmission. Methods for reducing transmission in

health care settings include the use of face masks, patient education about pulmonary hygiene, early diagnosis, and having appropriate availability of services or referral networks [1;173].

## Causes of Morbidity and Mortality in Coinfected Individuals

HIV and TB-coinfected patients have higher case fatality rates than HIV-uninfected patients with TB; case fatality rates greater than 10 percent have commonly been reported where there is a lack of access to HAART in resource-limited settings [174]. In one series reported from Puerto Rico, where three-quarters of the patients were IDUs, 55 percent died within the first year after diagnosis [175]. Case fatality rates are higher in sputum negative and extrapulmonary TB compared with pulmonary TB [9;174]. While it is often difficult to ascertain the cause of death, it appears that early mortality is more frequently related to TB, while deaths during the continuation phase of TB treatment are more commonly due to AIDS related conditions [176].

The commencement of HAART in HIV and TB-coinfected patients has been associated with significant reductions in occurrence of subsequent AIDS defining illness and approximately a 50 percent reduction in mortality at four years [141]. Virological responses to HAART have been reported as similar, however CD4 cell count increases after commencing HAART are smaller among patients who developed active TB than among those who remained free of TB [177].

HAART has been associated with a reduction in rates of active TB by an estimated 70–90 percent amongst HIV-infected patients [177–183]. However, active TB still continues to occur among HIV-infected patients on HAART at rates greater than amongst the general population [184]. In Europe and North America, HAART has been reported to reduce active TB incidence by approximately fivefold, with the greatest reduction occurring during the first six months of treatment [185]. A progressive decline in active TB incidence with increasing duration of HAART was also seen in a cohort of patients in South Africa [177]. It is unknown whether continued HAART beyond three years results in a further reduction in TB incidence, although from current evidence it seems unlikely that HAART alone will reduce the risk of active TB for HIV-infected persons back to that of the general population [186;187]. After commencement of HAART, the strongest predictor of development of active TB within the first six months of treatment is the baseline level of immunodeficiency as measured by the CD4 count [177;185]. After six months of treatment, risk factors for development of active TB while on HAART include the baseline CD4 count, and response to HAART as assessed at six months (CD4 count,

HIV RNA > 400 copies per ml and degree of increase in CD4 count compared with baseline CD4 count) [177;185;186].

## Conclusion

HIV and TB coinfection is a significant global problem that presents many challenges, which are even greater in IDUs. The increased risk for IDUs to acquire HIV and TB infection has fuelled both epidemics in many regions, emphasizing the need to improve treatment for IDUs on both an individual and public health basis. While effective treatment is available to cure TB and to reduce HIV-associated morbidity and mortality, there remain many dilemmas in the treatment of coinfecting patients who frequently have poorer outcomes. The optimal HAART regimens, dosing, and timing of commencement in combination with anti-TB medications require further study. Standard clinical guidelines often neglect the problems faced by the medical team treating active IDUs and there is a need for further research into the most effective methods of implementing and monitoring treatment of HIV-associated TB. Above all, patient centered management is essential in successful TB and HIV management for IDUs.

**Table 1.** Recommended Tuberculosis treatment for persons not previously treated\*

Preferred	INH, RIF, PZA, EMB daily, 2 months <sup>1</sup>	INH, RIF daily, 4 months
	INH, RIF, PZA, EMB 3x/wk, 2 months <sup>1</sup>	INH, RIF 3x/wk, 4 months
Optional	INH, RIF, PZA, EMB daily, 2 months	INH, EMB daily, 6 months <sup>2</sup>

1. Streptomycin may be substituted for ethambutol.

2. Associated with higher rate of failure and relapse and should ideally be avoided in HIV-infected patients.

\* Modified from standards cited in note 73.

**Table 2.** Suggested regimens for common TB drug resistance patterns\*

<i>Drug resistance pattern</i>	<i>Suggested regimen</i>	<i>Duration of treatment</i>
INH (+/-SM)	RIF, PZA, EMB	6 months
RIF	INH, EMB, FQN, supplemented with PZA for the first 2 months (an IA may be included for the first 2–3 months for patients with extensive disease)	12–18 months
INH + RIF (+/-SM)	FQN, PZA, EMB, IA +/- another agent	18–24 months

EMB = ethambutol; FQN = fluoroquinolone; IA = injectable agent (e.g. aminoglycoside or capeomycin); INH = isoniazid; PZA = pyrazinamide; RIF = rifampin; SM = streptomycin.

\* Modified from publication cited in note 76.

**Table 3.** Recommendations for coadministering rifampicin with protease inhibitors and NNRTIs

<i>Adverse effect</i>	<i>Anti-TB medication</i>	<i>Antiretroviral medication</i>
Gastrointestinal intolerance	Isoniazid, rifampicin, pyrazinamide	Zidovudine, didanosine, protease inhibitors
Hepatitis	Isoniazid, rifampicin, pyrazinamide	Nevirapine, efavirenz, protease inhibitors
Hypersensitivity reactions	Isoniazid, rifampicin	Abacavir
Peripheral neuropathy	Isoniazid	Didanosine, stavudine
Rash	Isoniazid, rifampicin	Nevirapine, efavirenz, amprenavir, abacavir
Neuropsychiatric difficulties	Isoniazid	Efavirenz
Bone marrow suppression	Rifampicin, rifabutin	Zidovudine

**Table 4.** Common overlapping side effects between anti-TB medications and antiretrovirals\*

<i>Rifamycin</i>	<i>Antiretroviral</i>	<i>Antiretroviral dose change</i>	<i>Comments</i>
Rifampicin 600 mg/day	Efavirenz	600 mg/day (some recommend increasing dose to 800 mg if > 60 kg )	Efavirenz AUC ↓ by 22%
	Nevirapine	200 mg twice daily (No safety data on increased dose of 300 mg twice daily)	Nevirapine AUC ↓ 37–58% Only use if no other options exist and close virological monitoring is possible. Concern regarding increased hepatotoxicity
	Ritonavir	No dose change	Ritonavir AUC ↓ by 35% Coadministration may → loss of virological response
	Saquinavir/ ritonavir	Saquinavir 400 mg + ritonavir 400 mg twice daily	Limited clinical experience Significant hepatotoxicity in 11 of 17 pts in phase 1 trial in healthy individuals with SQV 1000 mg + ritonavir 1000 mg twice daily
	Lopinavir/ ritonavir (Kaletra)	Lopinavir/ritonavir (Kaletra) 3 capsules + 300 mg ritonavir twice daily	Lopinavir AUC ↓ by 75% Limited clinical experience

Due to significant interactions, rifampicin should not be used in combination with the following protease inhibitors: amprenavir, atazanavir, indinavir, nelfinavir or with ritonavir boosted protease inhibitors except as mentioned above.

Rifampicin and delavirdine should not be used together.

\* Modified from guidelines cited in note 115.

**Table 5.** Recommendations for coadministering rifabutin with protease inhibitors and NNRTIs\*

<i>Rifamycin</i>	<i>Antiretroviral</i>	<i>Antiretroviral dose change</i>
Rifabutin 450 mg/day or 600 mg 3x/week	Efavirenz	No dose adjustment
Rifabutin 300 mg/day	Nevirapine	No dose adjustment
Rifabutin 300 mg 3x/week	Amprenavir or ritonavir	No dose adjustment
Rifabutin 150 mg/day	Indinavir	↑ to 1000 mg three times daily
	Nelfinavir	750mg three times daily or 1250 mg two times daily
	Atazanavir	400 mg daily
Rifabutin 150 mg 3x/week	Ritonavir boosted saquinavir, indinavir, ampenavir, atazanavir, lopinavir	No dose adjustment
Rifabutin and delavirdine should not be used together.		
Rifabutin and saquinavir should not be used together.		

\* Modified from guidelines cited in note 115.

**Table 6.** Suggested timing of HAART in HIV-infected persons receiving tuberculosis treatment. This table can be found on the WHO website (HIV department) as part of the WHO ART guidelines.

<i>CD4 Cell Count</i>	<i>HAART recommendations</i>	<i>Timing of HAART after start of TB treatment</i>
CD4 < 200 mm <sup>3</sup>	Recommend HAART	Between 2–8 weeks
CD4 between 200–350/mm <sup>3</sup>	Recommend HAART	After 8 weeks
CD4 > 350 mm <sup>3</sup>	Defer HAART	Re-evaluate patient at 2 months and end of TB treatment
CD4 not available	Recommend HAART	After 8 weeks



### 3. Drugs, Alcohol, and Antiretroviral Medicines



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Increasing numbers and newer classes of antiretrovirals have heightened awareness about the significance of drug interactions in the HIV population. However, recreational drugs are often not considered by clinicians and patients when reviewing a particular medication regimen. Given the rising incidence of HIV infection among substance users and the increasing use of complex antiretroviral regimens, the risk of adverse drug interactions cannot be overlooked or ignored.

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# Recreational Drugs and Opiate Substitution Medications: Interactions with Antiretrovirals

Tony Antoniou, Alice Lin-in Tseng\*

## Introduction

The advent of potent new therapies has seemingly turned the tide in the battle against HIV. Specifically, combinations of antiretroviral drugs that include a member of the protease inhibitor or non-nucleoside reverse transcriptase inhibitor family have significantly delayed the progression of the disease and death [1–3]. However, the addition of combination therapies to already complex medication regimens dramatically increases the likelihood of drug interactions [4–7]. Protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), in particular, have a propensity for causing

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drug interactions as a result of their ability to either inhibit or induce the cytochrome P450 (CYP450) enzyme system [8–13]. Newer drug classes under study including CCR5 antagonists (e.g., maraviroc, vicriviroc) and integrase inhibitors (e.g. GS-9137) are also substrates of the CYP3A4 system, and hence may also be subject to similar interaction concerns [8–13] (comprehensive summary reference tables of interactions between antiretrovirals, recreational drugs, and opiate substitution medications can be found at the end of this publication).

While numerous interactions of varying clinical significance have been well described with these antiretrovirals [10–12], less is known about the potential for drug interactions with recreational drugs. This is an issue of concern since a significant proportion of HIV-infected individuals may be at risk of experiencing potentially harmful interactions between antiretrovirals and legal or illegal psychoactive drugs.

Injection drug use remains a significant risk factor for the acquisition of HIV infection [14;15]. According to the Centers for Disease Control and Prevention, the proportion of AIDS cases in the United States associated with injection drug use has increased from 12 percent in 1981 to 24 percent by the end of 2004 [16]. In Canada, 30 percent of new HIV infections were attributable to injection drug use in 2002 [17]. The proportion of HIV/AIDS cases attributable to injection drug use is even more pronounced in other parts of the world, accounting for 65 percent of new HIV diagnoses in Eastern Europe in 2004, and over 80 percent of all HIV cases in Russia through 2004 [18]. In China, injection drug use was associated with 42 percent of all HIV cases through 2004 [19]. These data underscore the global extent to which injection drug use remains a significant risk factor for HIV transmission.

Furthermore, the effects of injection and non-injection drug use can lead to behaviors and practices that are driving forces behind HIV transmission. Drug induced feelings of euphoria and disinhibition often compromise judgement and critical thinking. Drug users may also be enticed or coerced into trading sex or engaging in unprotected sex work to get access to drugs. Finally, drug use can interfere with an individual's ability to adhere to antiretroviral treatment, and reduce their chances of successfully pursuing therapy.

Many prescription, non-prescription, and recreational drugs undergo extensive hepatic metabolism via cytochrome P450 isoenzymes and/or glucuronidation. Thus, there is potential for significant interactions between these agents and antiretrovirals, particularly PIs and NNRTIs. Concentrations of many recreational drugs may be significantly increased or decreased in the presence of these antiretrovirals, and may be associated with serious, adverse outcomes.

Several years ago, a report of a suspected fatal interaction between ritonavir and 3,4-methylenedioxymethamphetamine (MDMA, also known as “ecstasy”) sparked demands for increased awareness and research in this area [20]. Unfortunately, to date, few formal interaction studies in this field have been conducted due to considerable social and

legal barriers. In the absence of controlled, scientific pharmacokinetic interaction data in humans, potential interactions may be postulated using *in vitro* and *in vivo* drug metabolism data [21;19]. Since many recreational drugs are metabolized to some degree by the cytochrome P450 system, it is reasonable to anticipate that concomitant use with PIs and delavirdine could possibly result in drug accumulation and/or toxicity. Similarly, treatment with enzyme inducers such as the NNRTI nevirapine or the PI tipranavir may precipitate withdrawal reactions to recreational agents metabolized by the cytochrome P450 system. Interactions between the NNRTI efavirenz and recreational drugs may be more difficult to predict, given that efavirenz can both inhibit (3A4, 2C9/19) and induce (3A4) selected isoenzymes of the cytochrome P450 system, although induction of 3A4 appears to predominate over inhibition of this particular isoenzyme [7;13].

Given the continued paucity of data regarding recreational drugs and antiretrovirals, this review aims to summarize actual, observed, or hypothetical interactions between these drugs based on existing human interaction studies, case reports, and *in vitro* or *in vivo* pharmacokinetic data. General information regarding the steps involved in drug metabolism is reviewed elsewhere [21]. Suggestions on management or avoidance of potential interactions are also provided. Finally, summary interaction tables can be found at the end of this publication.

## “Rave Drugs”—MDMA, Amphetamines, GHB, Ketamine, LSD, and PCP

Commonly known as “ecstasy,” “XTC,” “Adam,” and “Essence,” 3, 4-methylenedioxy-methamphetamine (MDMA) is a widely used substance at all-night dance parties known as raves and is also increasingly being used recreationally by young professionals. Taken orally as a capsule or tablet at average doses of 75–100 mg [22], users cite MDMA as enhancing feelings of empathy for others, anxiolysis, and strong feelings of euphoria. MDMA is an amphetamine-like compound that is metabolized by the cytochrome P450 system. Specifically, demethylenation to 3,4-dihydroxymethamphetamine (HHMA) is thought to occur via the CYP2D6 isoenzyme [23–25]. Although this isoenzyme accounts for 50–60 percent of MDMA metabolism *in vitro*, CYP2D6 accounts for only 30 percent of MDMA metabolism *in vivo* [26]. Other isoforms, including CYP3A4, CYP2B6, and CYP1A2 contribute to MDMA metabolism *in vitro*, and likely contribute to the *in vivo* metabolism of MDMA, given the considerable demethylenation of MDMA observed despite CYP2D6 inhibition by paroxetine [26]. Concomitant administration with CYP450 inhibitors could therefore lead to significant increases in MDMA exposure with potentially dangerous and even fatal consequences, as illustrated by the case report below.

Within a few hours of taking 180 mg of MDMA, a 32-year-old male with AIDS experienced symptoms suggestive of a heightened serotonergic state, including tachypnea, tachycardia, cyanosis, and profuse sweating. He then experienced an apparent tonic-clonic seizure, increased tachypnea and tachycardia (carotid pulse was approximately 200 per minute), and subsequently died from a cardiorespiratory arrest. This patient had previously taken similar amounts of MDMA on several occasions without adverse effects, but this was the first time he had taken MDMA since adding ritonavir 600 mg twice daily to his antiretroviral regimen. At autopsy, the patient's blood levels of MDMA were approximately tenfold higher than expected, given the amount of MDMA ingested. Since ritonavir is a well-known potent inhibitor of many hepatic isoenzymes including CYP2D6, the clinicians concluded that the patient likely experienced a fatal serotonergic reaction to MDMA as a result of an interaction with ritonavir [20]. The danger associated with this interaction may be magnified due to the large variability in the actual amount of MDMA between tablets and the presence of other chemicals (e.g. amphetamines, ephedrine) in some MDMA tablets whose metabolism can also be inhibited by ritonavir with life-threatening consequence [27]. Thus, the combination of MDMA and ritonavir should be avoided if possible. Other isoforms of the cytochrome P450 system may also be involved in the metabolism of MDMA, notably 1A2, 2B6 and 3A4 [25]. All protease inhibitors can inhibit CYP3A activity to varying degrees, and ritonavir, nelfinavir, and efavirenz also demonstrate inhibitory activity against 2B6 [28]; therefore, individuals using MDMA should be warned about the potential for an interaction with these agents, and be advised to take appropriate precautions (e.g. use about one-quarter the usual amount of MDMA, take breaks from dancing, ensure that the rave or party has a medical team on site, and maintain adequate hydration by avoiding alcohol and replenishing fluids regularly).

Other amphetamines, particularly methamphetamine ("Crystal meth," "speed"), are used at raves. These drugs are also mainly metabolized by the 2D6 isoenzyme of the cytochrome P450 system [29–31]. Thus, potentially dangerous interactions with therapeutic doses of ritonavir may be observed. Although data describing the potential for a pharmacokinetic interaction between methamphetamine and protease inhibitors are lacking, a case of a potentially fatal interaction between methamphetamine and ritonavir has been published [32]. In this account, a 49-year-old HIV-positive male receiving ritonavir 400 mg twice per day, saquinavir 400 mg twice per day, and stavudine 40 mg twice per day died following the use of injected methamphetamine. Toxicological analysis indicated that blood levels of methamphetamine in this patient measured 0.5 mg/l, well within the fatal range of this agent [33]. However, the role of ritonavir mediated inhibition of methamphetamine metabolism in this case is confounded somewhat by the presence of concomitant recreational drug use, as cannabinoids and traces of benzodiazepines were also detected upon toxicologic analysis of the patient's blood. Still, given

the potential for fatal increases in the concentration of amphetamines with concomitant ritonavir, the combination should be avoided if possible.

Gamma hydroxy-butyrate (GHB), also known as “liquid ecstasy,” “grievous bodily harm” or “G,” is a naturally occurring metabolite of the neurotransmitter GABA that is used at raves for its euphoric effects and among body-builders for its perceived growth hormone releasing effects [34]. Colorless, odorless, and tasteless, GHB has also been used in the context of date rape when slipped into beverages. Although illegal in the United States, GHB is used as a general anesthetic in Europe and has been demonstrated to improve abstinence rates in alcoholic subjects [35]. The pharmacokinetics of GHB have not been well characterized. The major route of elimination is expired breath as carbon dioxide, although animal data suggest that first pass metabolism may also play a large role in GHB clearance [36;37]. Since first pass metabolism is often mediated by the cytochrome P450 system, it is possible that inhibitors of this system could predispose patients to GHB-related toxicity. As the precise metabolic pathway involved in the metabolism of GHB is unknown, patients who use GHB should be warned about the potential dangers of a drug interaction with PIs (especially ritonavir), delavirdine, and possibly efavirenz. The potential for a GHB interaction is highlighted by a report of an HIV-positive patient on ritonavir and saquinavir who developed symptoms consistent with GHB toxicity shortly following the ingestion of a small amount of GHB (estimated at approximately 10 mg/kg). The patient had ingested the GHB to counter the agitating effects of two MDMA tablets, which had lasted much longer (29 hours) compared to when he had used MDMA prior to initiating antiretroviral therapy [38]. Since the patient had taken similar doses of both MDMA and GHB without incident prior to initiating therapy with ritonavir and saquinavir, the authors concluded that PI mediated inhibition of MDMA and GHB was responsible for the adverse reactions noted.

Ketamine, also known as “Special K” or “kit kat,” may be used at raves for its dissociative, intoxicating, and amnesic properties. Users may inhale the powder form, while ketamine liquid is usually added to drinks and ingested orally. The main route of ketamine metabolism is N-demethylation to norketamine, a metabolite with approximately one-third the anesthetic activity of its parent compound. Norketamine is then hydroxylated and conjugated to water soluble conjugates that are excreted in the urine [39]. The 2B6 isoform of the cytochrome P450 system appears to be the main enzyme involved in ketamine metabolism, with 3A4 and 2C9 involved to a lesser extent [40]. There are no studies or case reports of interactions between ketamine and antiretroviral agents. However, since ritonavir, nelfinavir, and efavirenz are potent inhibitors of the 2B6 isoenzyme, patients who use ketamine recreationally may be at risk for ketamine toxicity due to drug accumulation. Animal studies suggest that ketamine may itself be a weak inhibitor of CYP3A4 [41;42], although the clinical significance of this is unclear in the absence of human data. Still, until such results can be confirmed, it may be prudent

to avoid recreational ketamine use while taking drugs that are CYP3A4 substrates and have narrow safety thresholds (e.g. cisapride, terfenadine, astemizole).

Phencyclidine (PCP), known on the street as “angel dust,” “rocket fuel” or “killer weed,” may be used at raves for its hallucinogenic or dissociative properties. Users may also report feelings of empowerment and invulnerability with PCP use. PCP is metabolized in the liver through oxidative hydroxylation, with up to five metabolites being formed. The 3A4 isoform of the cytochrome P450 system appears to play a major role in the hydroxylation of PCP [43]. Results from previous rat model studies also suggest that CYP2C11 may be involved in PCP metabolism [44], and that CYP2B1 may be inhibited *in vitro* [45]. Thus, it would be expected that concurrent use of PCP with PIs, delavirdine, and possibly efavirenz may result in elevated PCP levels, and resultant toxicity. Patients using PCP who are also receiving treatment with antiretrovirals should be cautioned to use less than what they would normally use, given the potential for a drug interaction.

Lysergic acid diethylamide (LSD), is also known popularly as “acid” or “blotters” since it may be used in the form of paper microdots for its hallucinogenic and mild euphoric properties. Although the cytochrome P450 system may be involved in the metabolism of LSD, the exact contribution of this system in overall LSD clearance and the isoenzymes involved have not been detailed [46;47]. Thus, anticipating drug interactions with LSD is extremely difficult. Patients who use LSD recreationally and who receive treatment with antiretrovirals should be cautioned about the possibility of an interaction, and to be familiar with signs of LSD toxicity and perhaps consider using a smaller amount than normal. Tables summarizing the interactions between rave drugs and antiretrovirals can be found at the end of this publication [20; 23–25;27–31,36–43;46;47].

## Methadone

Since methadone is metabolized extensively by various isoenzymes of the cytochrome P450 system, including CYP3A4, CYP2B6, CYP2D6, and 2C19, the likelihood of interactions with NNRTIs and PIs is high [48–51]. Several such interactions have been described in the literature and are summarized in Table 3 at the end of this publication. As expected, patients maintained on methadone who are subsequently treated with either efavirenz or nevirapine are at risk of developing opiate withdrawal symptoms due to NNRTI-mediated enzyme induction of CYP3A4 and CYP2B6. Such patients may require an increase in their methadone dose, although the magnitude of the dose increase may not always parallel the reduction in total methadone exposure. For example, data by Clarke and colleagues suggest that despite a decrease of over 50 percent in methadone area under the

curve (AUC) seen with the addition of efavirenz, a mean increase in methadone dose of only 22 percent (in 10 mg increments) was required to counteract symptoms consistent with opiate withdrawal [52]. A similar interaction has been described between nevirapine and methadone, in that a mean increase in methadone dose of 16 percent was required to compensate for a 50 percent reduction in methadone AUC [75].

Interactions between PIs and methadone have been even less predictable. In vitro, the AUC for methadone increased twofold when administered with ritonavir and 30 percent when administered with indinavir [79]. A later study in healthy volunteers did not confirm these findings, noting a decrease in the AUC of methadone of 36 percent with concomitant ritonavir [80]. However, these results are somewhat limited since only a single 5 mg dose of methadone was studied. Similarly, reduced methadone levels have been noted in the presence of lopinavir/ritonavir [77] and nelfinavir [60]. These observations suggest that ritonavir, nelfinavir, and possibly lopinavir may be inducing an alternative route of methadone metabolism [59;64;65].

Reduced methadone levels have not always been accompanied by symptoms of opiate withdrawal. This lack of correlation between levels and clinical withdrawal may be related to a disproportionately larger induction in the metabolism of methadone's inactive S-(+)-enantiomer, as opposed to the R-(-) enantiomer, which harbors essentially all opiate activity [61]. Further studies need to be conducted between methadone and PIs to better clarify the nature of these interactions. Clinicians should be prepared for the possibility that some patients stabilized on methadone might require a dose increase when either nelfinavir or ritonavir is introduced.

Interactions between methadone and the reverse transcriptase inhibitors zidovudine, didanosine, and stavudine have also been described. Overall, methadone appears to increase total exposure to zidovudine. The mechanisms underlying this interaction appear to involve inhibition of zidovudine glucuronidation, and to a lesser extent, decreased renal clearance of zidovudine. Although the clinical implications of these findings are unclear, patients receiving the combination of methadone and zidovudine should be monitored for zidovudine-related toxicities such as nausea, vomiting, headaches, and myelosuppression [67;68]. Since many of these symptoms may mirror those of opiate withdrawal, patients may confuse the symptoms of zidovudine toxicity with a requirement for a higher methadone dose. However, methadone levels do not appear to be altered by concomitant zidovudine administration, thereby discounting the association of such symptoms with opiate withdrawal.

In contrast to zidovudine, methadone appears to decrease levels of both stavudine and didanosine buffered tablets, possibly by delaying absorption of these agents and thereby allowing enhanced time for enzymatic or acid-catalyzed degradation. Since didanosine is more prone to acid-catalyzed degradation than stavudine, the impact of methadone on didanosine levels is more pronounced than for stavudine [66]. However,

intracellular levels of ddATP were not measured, nor was virologic or immunologic outcome addressed.

A subsequent study comparing didanosine buffered tablets and didanosine enteric coated capsules in HIV-negative participants on methadone noted a trend toward decreased didanosine concentrations with didanosine buffered tablets in the presence of methadone. However, when didanosine capsules were administered, didanosine plasma concentrations were not changed in the presence of methadone compared to historical control data. Thus, enteric coated didanosine capsules may be coadministered with methadone without dosage adjustment [81].

As well as being a substrate of the CYP450 system, methadone can also act as an inhibitor of the 2D6 and 3A isoforms [82–84]. It is therefore possible that concomitant use of methadone and PIs or NNRTIs may result in increased antiretroviral levels, and predispose patients to drug specific adverse events. However, methadone did not alter the pharmacokinetics of delavirdine, a 3A4 substrate [70]. In addition, aside from a reduction in levels of the pharmacologically active M8 metabolite, significant changes to the pharmacokinetics of nelfinavir were not observed with concomitant methadone [72]. The metabolism of nelfinavir to its M8 metabolite is mediated by the 2C19 isoenzyme of the P450 system, suggesting that methadone may inhibit this isoenzyme as well. Although virologically active, a reduction in M8 levels does not appear to be clinically significant [85]. Thus, significant elevations in the levels of PIs and NNRTIs may not occur with methadone. Still, the impact of methadone on other members of these classes is unknown, and, as with zidovudine, it may be difficult to discriminate between symptoms associated with PI toxicity (e.g. nausea, vomiting, diarrhea) and methadone withdrawal. However, since enzyme inhibition is an acute process, while enzyme induction occurs following several days of drug administration, it may be possible to distinguish the two interactions based on the time course of symptom development. That is, symptoms which develop within two to three days of concomitant administration may be due to PI toxicity, whereas those which develop after six days onward are more likely to be related to opiate withdrawal.

## Buprenorphine

Buprenorphine is a partial opioid agonist that is a safe and effective alternative to methadone for the management of opioid dependence [86;87]. Buprenorphine is extensively metabolized in the liver by dealkylation to the metabolite norbuprenorphine, which possesses approximately one-fiftieth of the analgesic potency of the parent drug [88]. The overall contribution of norbuprenorphine to the therapeutic efficacy of buprenorphine

is therefore thought to be low. The CYP450 enzyme system is heavily involved in this reaction, with the CYP3A4 and CYP2C8 isoenzymes responsible for approximately 65 percent and 30 percent of norbuprenorphine production, respectively [89]. Norbuprenorphine is metabolised by glucuronidation. It is therefore reasonable to assume that a large potential for interactions exists between inducers and inhibitors of the CYP3A4 system and buprenorphine. Specifically, inhibition of the CYP3A4 pathway by protease inhibitors or delavirdine would substantially decrease the metabolism of buprenorphine, and predispose patients to potential opiate toxicity. However, relative to interactions with other CYP3A4 substrates, the presence of an alternative metabolic pathway and a ceiling effect with respect to opioid agonist activity may temper the toxicity associated with interactions between CYP3A4 inhibitors and buprenorphine. To date, there are no pharmacokinetic studies addressing this question. However, *in vitro* studies confirm the potential for both ritonavir and indinavir to significantly inhibit buprenorphine metabolism [90]. Furthermore, a recent case report noted symptoms of opiate toxicity in three subjects taking atazanavir 300 mg/ritonavir 100 mg once daily with buprenorphine. In all cases, symptoms improved with reduction of buprenorphine to a lower daily or every other day dose. The authors postulated that the potential mechanism may be due to CYP3A4 inhibition by atazanavir or ritonavir, or inhibition of glucuronidation by atazanavir [91]. Until further data are available, buprenorphine should be initiated at reduced doses in subjects receiving protease inhibitor therapy. Buprenorphine dosage should be titrated slowly and close monitoring for signs and symptoms of opiate toxicity is recommended.

In contrast, CYP3A4 inducers such as nevirapine, efavirenz or tipranavir may expedite buprenorphine metabolism and precipitate symptoms of opiate withdrawal. To date, there are no data describing the potential for an interaction between nevirapine and buprenorphine. In a study of 15 HIV-negative opioid-dependent patients who had received therapy with buprenorphine for two weeks, the addition of efavirenz 600 mg per day for 15 days resulted in a 50 percent decrease in the AUC of buprenorphine [92]. Although no episodes of opiate withdrawal were observed in this study, continued monitoring for withdrawal symptoms is warranted when efavirenz and buprenorphine are coadministered on a chronic basis until these data are confirmed by larger studies with longer follow-up.

Although *in vitro* data suggest that both buprenorphine and norbuprenorphine can act as inhibitors of CYP2D6 and CYP3A4, and thereby potentially modulate the pharmacokinetics of antiretrovirals, the concentrations at which such inhibition was noted exceed those that are used clinically [93]. Thus, buprenorphine mediated changes in levels of PIs or NNRTIs are not expected. Similarly, unlike methadone, administration of combined buprenorphine-zidovudine therapy in 17 patients did not result in increases in zidovudine exposure relative to zidovudine therapy alone [94]. Increases

in the frequency and/or severity of zidovudine toxicity with buprenorphine therapy are therefore not anticipated.

## Meperidine (Demerol)

Two pathways are involved in meperidine metabolism: hydrolysis to meperidinic acid by liver carboxylesterases and demethylation to normeperidine by microsomal enzymes. Demethylation to normeperidine is mediated principally by CYP2B6, with lesser contributions made by the 3A4 and 2C19 isoenzymes [95]. Given the low expression levels of CYP2C19 in the human liver, it is likely that CYP2B6 and CYP3A4 account for the majority of normeperidine formation [95]. In patients with renal failure or with frequent dosing, normeperidine can accumulate and lead to CNS excitatory toxicity.

In an open label study, eight HIV-negative volunteers received 50 mg meperidine prior to and following 10 days of treatment with escalating doses of ritonavir. Meperidine AUC decreased 67 percent in the presence of ritonavir ( $p < 0.005$ ) while normeperidine AUC increased 47 percent, suggesting that ritonavir induces the metabolism of meperidine to normeperidine [96]. However, since normeperidine has some pharmacologic activity, the potential for decreased analgesic effect and risk of opiate withdrawal may be lessened. On the other hand, because normeperidine possesses excitatory CNS effects, patients who use meperidine and ritonavir concomitantly may be at increased risk of seizures. Patients with renal failure may also be at increased risk of CNS excitatory toxicity due to normeperidine accumulation.

## Morphine

Although the CYP450 system is not extensively involved in the metabolism of morphine, interactions between morphine and certain antiretrovirals are nonetheless still possible. Morphine is metabolized principally by glucuronidation to one of two main metabolites. The chief route of metabolism is via the UGT1A3 and UGT1A8 isoenzymes of the UDP-glucuronyltransferase system to generate morphine-3-glucuronide, a metabolite essentially devoid of opiate activity [97]. Morphine-6-glucuronide (M6G), a metabolite with up to 50 times the analgesic potency of morphine, is generated by the UGT2B7 isoform of the UDP-glucuronyltransferase system [97–100]. As inducers of the UDP-glucuronyltransferase system, nelfinavir, ritonavir, and tipranavir may alter the metabolic disposition of morphine. Although the exact isoforms of the UDP-glucuronyltransferase

system affected by these PIs are unknown, it can be inferred that the UGT2B7 enzyme is induced by nelfinavir, ritonavir, and tipranavir, given the decrease in concentrations of the UGT2B7 substrate zidovudine observed with the concomitant administration of these agents [101;102;103]. It is therefore possible that induction of the UGT2B7 system by nelfinavir or ritonavir may increase the generation of the active M6G metabolite, thereby increasing morphine efficacy and/or increasing the risk of adverse reactions. Although morphine concentrations would be reduced by UGT2B7 induction, the generation of increasing concentrations of active metabolite with enhanced potency may offset the effects of a decrease in parent drug levels. There are thus far no pharmacokinetic studies or case reports describing the effects of nelfinavir or ritonavir on morphine disposition. Postulated interactions between morphine and antiretrovirals are summarized in Table 4 at the end of this publication [97–100].

Although morphine itself is an inhibitor of the UGT2B7 isoenzyme, interactions with zidovudine are unlikely, given the weak nature of this inhibition [104;105].

## Codeine, Oxycodone, and Hydrocodone

As with morphine, the principal route of codeine metabolism is via glucuronidation by the UGT2B7 and UGT 2B4 isoenzymes of the UDP-glucuronyltransferase system [106;107]. The ensuing metabolite, codeine-6-glucuronide (C6G), accounts for approximately 70 to 80 percent of codeine metabolism. Relatively minor routes of codeine metabolism are CYP3A4 mediated generation of norcodeine and CYP2D6 mediated formation of morphine [108;109]. Although conversion to morphine accounts for < 10 percent of codeine metabolism in most studies, it is the CYP2D6 catalyzed generation of morphine that is thought to be most responsible for the analgesia attributable to codeine [108;109]. Therefore, administration of agents that modulate codeine disposition such that morphine generation is compromised may decrease the efficacy of this drug and/or lead to withdrawal symptoms. There are several theoretical ways by which antiretroviral agents can modulate codeine metabolism in this manner [110–113]. Direct inhibition of the CYP2D6 isoenzyme by the concomitant administration of therapeutic doses of ritonavir is the most obvious means by which the generation of morphine from codeine may be reduced. Alternative scenarios include induction of the CYP3A4 isoenzyme by either nevirapine, efavirenz, or tipranavir, or induction of UGT2B7 by nelfinavir, tipranavir, or ritonavir. In either case, less substrate remains available for CYP2D6 mediated conversion to morphine. In contrast, inhibition of the CYP3A4 isoenzyme by concomitant administration of delavirdine or PIs may increase the yield of morphine, since more substrate is available for the CYP2D6 route of metabolism. Such

patients may be at inadvertent risk of opiate toxicity, although more substrate would also presumably be available for glucuronidation by UGT2B7, thereby potentially offsetting this risk. Thus far, no pharmacokinetic studies or case reports describing changes in codeine disposition with combined antiretroviral use have been published.

Similar to codeine, hydrocodone is metabolized by CYP2D6 to the more active opiate agonist hydromorphone and CYP3A4 to norhydrocodone [114]. Although hydromorphone binds to  $\mu$ -opiate receptors with an affinity that is up to thirty-threefold greater than that of hydrocodone, the degree to which CYP2D6 metabolism is critical to attaining analgesia from hydrocodone is not known. It is therefore unclear what impact the concomitant administration of antiretrovirals would have on therapeutic response to hydrocodone [115;116]. Theoretically, inhibition of CYP2D6 mediated metabolism by therapeutic doses of ritonavir or induction of CYP3A4 by nevirapine, efavirenz or tipranavir may compromise the efficacy of hydrocodone and/or elicit symptoms of opiate withdrawal. Similarly, inhibition of the CYP3A4 pathway may increase the amount of substrate available for CYP2D6 generation of hydromorphone, potentially increasing the risk of opiate toxicity. However, since approximately 40 percent of hydrocodone metabolism occurs via non-CYP based metabolism [114], the presence of an alternative route of hydrocodone elimination may offset the risk of opiate toxicity somewhat in the presence of CYP3A4 inhibitors. Formal pharmacokinetic studies between antiretrovirals and hydrocodone are clearly necessary to better elucidate changes in metabolite disposition and pharmacodynamic response with combined use.

As with hydrocodone, oxycodone is metabolized in a similar manner to yield oxymorphone (CYP2D6) and noroxycodone (CYP3A4), with N-demethylation to noroxycodone representing the predominant route of metabolism [117]. However, since oxycodone itself is known to be a potent analgesic, CYP2D6 mediated O-demethylation to a morphine congener is not critical to the analgesic potency of this agent [118]. Potential interactions between codeine, hydrocodone, oxycodone, and antiretrovirals are summarized in Table 4 at the end of this publication.

## Cocaine and Heroin

The significant role played by cocaine in the transmission of HIV cannot be underestimated. While injecting cocaine or heroin puts users at risk of acquiring HIV through contaminated syringes, smoking “crack” cocaine may independently be associated with acquisition of HIV infection through its association with high-risk sexual practices such as the exchange of drugs for sex [99;119;120]. Since patients who acquire HIV in the

context of crack or cocaine use may continue their drug use practices, an understanding of the potential for interactions with antiretrovirals is important.

Cocaine is metabolized chiefly by one of three pathways [121]. Spontaneous hydrolysis of cocaine to benzoylecgonine accounts for approximately 39 percent, 30 percent, and 16 percent of a single dose of cocaine administered by intravenous, intranasal, and smoked routes, respectively [122]. Degradation by serum and hepatic cholinesterases to ecgonine methyl ester can account for up to 32 to 49 percent of an administered cocaine dose [121;123]. Finally, N-demethylation to norcocaine, mediated by the 3A4 isoform of the cytochrome P450 system, makes up less than 10 percent of cocaine's biotransformation [121;124;125]. Other metabolites (e.g. anhydroecgonine methyl ester, p-hydroxy cocaine, etc.) are also produced in the metabolism of cocaine, although in smaller amounts.

Interactions between cocaine and antiretrovirals have not been described. Theoretically, inhibition of CYP3A4 may increase levels of the parent compound by blocking a route of cocaine metabolism. However, given that N-demethylation is a relatively small component of cocaine metabolism, such an interaction would not be expected to increase the risk of cocaine toxicity. An exception may occur in patients who are also cholinesterase deficient, since they lack the complementary enzymes necessary to metabolize the excess cocaine burden [126].

Inhibition of the CYP3A4 isoform would consequently result in decreased production of norcocaine; norcocaine is thought to play a critical role in mediating the hepatotoxicity of cocaine [127;128]. In vitro studies documenting the protective effect of 3A4 inhibitors against cocaine elicited hepatotoxicity lend credence to this notion [129]. Thus, it is possible that inhibition of 3A4 by some antiretrovirals may theoretically ameliorate the hepatotoxicity associated with cocaine, although it should be stressed that there are no clinical data to support this. Furthermore, such postulated effects may not be clinically significant in the context of other factors, such as concomitant hepatitis B or C infection.

However, if inhibition of 3A4 is theoretically protective against cocaine-mediated liver injury, the reverse may be true. That is, induction of CYP3A4 by nevirapine, efavirenz or tipranavir may lead to increasing amounts of norcocaine being formed, potentially increasing the risk of hepatotoxicity. Again, further research is necessary to clarify the nature and consequences of interactions between enzyme inducers and cocaine.

Heroin is rapidly metabolized to 6-monoacetylmorphine and morphine by plasma and liver esterases, respectively. Maximal blood levels of heroin and 6-monoacetylmorphine are attained within minutes and are cleared rapidly, while morphine levels rise and decrease more slowly [130;133]. Thus, potential interactions of concern may be similar to those noted with morphine (see Table 4 at the end of this publication).

## Benzodiazepines

Benzodiazepines remain among the most commonly prescribed psychotropic drugs. In Canada, the overall prevalence of benzodiazepine use for anxiolysis in the 1990s was estimated at roughly 8 percent of the adult population, while about 2.5 percent of adults were prescribed this group of drugs for insomnia [134]. Benzodiazepines may be used recreationally either alone or, more commonly, in the setting of multiple drug abuse. Potential abuses of benzodiazepines include moderating the effects of stimulants, allaying withdrawal symptoms from other recreational substances, acting as disinhibitory agents or augmenting the effects of other recreational drugs. As a class, benzodiazepines are extensively metabolized by the liver, with individual agents metabolized predominantly by either the CYP450 system or glucuronyltransferases.

Midazolam, triazolam, and alprazolam are metabolized mainly by the CYP3A4 isoenzyme [135;136]. Interactions with PIs, delavirdine, and possibly efavirenz are thus likely to produce increased levels of these compounds and place patients at risk of toxicity such as extreme sedation and respiratory depression. Pharmacokinetic studies and case reports documenting such interactions are summarized in Table 5 at the end of this publication [137–141]. It is interesting to note that conflicting data exist regarding the interaction between alprazolam and ritonavir. While Frye and colleagues noted a reduction in alprazolam exposure and relatively little change in pharmacodynamic effect following twelve days of ritonavir [137], subsequent work by Greenblatt and colleagues found that acute exposure to ritonavir reduced alprazolam clearance and enhanced alprazolam's pharmacodynamic properties [138]. This discrepancy may be accounted for by the fact that ritonavir, over time, may induce as well as inhibit CYP3A4 [142]. Thus, acute exposure to ritonavir may place patients at increased risk of alprazolam toxicity, while longer-term exposure to ritonavir may result in a loss of anxiolysis and possible withdrawal in patients who are using alprazolam recreationally. A longer-term study is necessary to further clarify the time course and nature of the interaction between alprazolam and ritonavir. Similarly, additional information is required to clarify the safety of using midazolam with PIs. Palkama and colleagues concluded that, aside from the possibility of a longer sedative effect, the use of bolus doses of intravenous midazolam with saquinavir is likely safe [139]. However, Merry and colleagues reported on a patient who experienced prolonged sedation secondary to the combination of midazolam and saquinavir; their experience warrants that patients receiving the combination should be closely monitored [140]. Data with other PIs are lacking. The use of midazolam with PIs and delavirdine should be avoided if possible, given the risk of prolonged sedation and respiratory depression associated with large increases in midazolam levels. Although formal pharmacokinetic studies are lacking, similar interactions between clonazepam and flunitrazepam

and protease inhibitors are possible, since both agents are substrates of CYP3A4 [143;144]. As well, caution should be exercised with diazepam, particularly in combination with ritonavir, since both the 3A4 and 2C19 systems appear to be important in its metabolism [145;146]. In contrast, nevirapine, efavirenz or tipranavir may put patients who are using midazolam, triazolam, alprazolam, clonazepam, and flunitrazepam at risk for loss of effect and/or withdrawal, due to their 3A4 inductive potential.

Interactions between lorazepam, oxazepam or temazepam and antiretrovirals will differ from those described above, since these members of the benzodiazepine family are metabolized primarily by glucuronidation [147;148]. Thus, drugs which increase the activity of glucuronyltransferases (i.e. ritonavir, nelfinavir) may accelerate the metabolism of these compounds, resulting in lower drug exposure. Although reports are lacking, concomitant use of lorazepam, oxazepam or temazepam with either ritonavir or nelfinavir may decrease the anxiolytic effect of these agents or precipitate symptoms consistent with a benzodiazepine withdrawal reaction due to the aforementioned interaction. A higher dose of the benzodiazepine may be necessary to compensate for the interaction.

## Tetrahydrocannabinol (THC)

THC, the active ingredient of smoked marijuana, remains a commonly used recreational agent. In Canada, 23.1 percent of surveyed adults had used marijuana more than once in their lives, and current use was estimated at 7.4 percent [149]. In the context of HIV/AIDS, smoked marijuana or THC containing preparations may also be used for anti-emetic or appetite stimulation purposes.

THC is metabolized in humans by microsomal oxidation to several hydroxylated metabolites, among them, 11-hydroxy-THC, which is pharmacologically active. Levels of 11-hydroxy-THC vary with the route of administration, with oral administration generally producing more of the active metabolite than inhaled THC due to significant first pass effect. Limited data suggest that CYP3A and 2C9 isoenzymes are involved in microsomal oxidation of THC [150–153]. Although inhibition of CYP3A4 or 2C9 may decrease the formation of pharmacologically active metabolite, the effects of THC are unlikely to be significantly attenuated, as THC itself is active and will be more bioavailable. Increased THC levels may lead to dose-related effects, including frank hallucinations, delusions, paranoid thinking, accentuation of altered time sense, anxiety, panic, depersonalization, loss of insight, orthostatic hypotension, and increased heart rate. Furthermore, inhibition of THC metabolism to 11-hydroxy THC may only be important in the setting of oral administration, since only trace amounts of the active metabolite are present following the smoked route.

Induction of CYP3A4 may increase the formation of pharmacologically active metabolite; however, the conversion of active metabolite to its inactive counterparts may also be accelerated, thereby decreasing the duration of THC effect. This may be more clinically important with oral THC administration, due to its large first pass effect.

The impact of THC on the pharmacokinetics of indinavir and nelfinavir has been evaluated in a small, randomized, placebo-controlled study. Patients on stable indinavir or nelfinavir therapy were randomized to receive either 3.95 percent THC cigarettes, THC 2.5 mg capsules or placebo, each administered three times a day. Nelfinavir and indinavir levels were determined prior to and on day 14 of THC use. A statistically significant 14 percent reduction in indinavir  $C_{max}$  was observed with smoked THC. As well, smoked THC significantly reduced the ratio of M8 (active metabolite of nelfinavir) to nelfinavir by 18 percent. However, as mentioned previously, reductions in M8 levels do not appear to be clinically important. Furthermore, a significant reduction in M8 levels relative to baseline was observed in patients receiving placebo. Other variables did not change significantly, nor did oral THC produce significant changes in indinavir or nelfinavir pharmacokinetics [154]. In addition, detrimental changes in immunologic and virologic parameters were not observed following short-term use of oral or smoked cannabinoids [155]. The long-term clinical consequence of these changes is likely negligible, especially with the increasing use of boosted protease inhibitor regimens. There are no reports documenting the impact of antiretrovirals on THC pharmacokinetics or pharmacodynamics. The nature of such an interaction would be difficult to predict, as several variables, including route of administration and the concentration of THC smoked may confound the outcome.

Considering the widespread use of smoked and oral THC derivatives for appetite stimulation and control of nausea and vomiting, and the lack of reports documenting deleterious effects secondary to the combination of THC and PIs, a clinically significant drug interaction may not exist when THC is used in moderate amounts. Patients who use THC and are beginning antiretrovirals should be warned about a possible accentuating of the effects of THC, and that they may need to use less THC for the same effect following treatment initiation.

## Alcohol

Ethanol metabolism is mediated chiefly by the enzymes alcohol dehydrogenase (formation of acetaldehyde) and aldehyde dehydrogenase. Since one of the two main metabolites of abacavir is a carboxylate derivative, the formation of which is catalyzed by the alcohol dehydrogenase enzyme, an interaction between ethanol and abacavir is possible

due to competition for metabolism. A randomized, open label, cross over study confirms the existence of such an interaction. Twenty-five HIV-positive patients were randomized to receive either a single 600 mg dose of abacavir, 0.7 g of ethanol per kilogram of body weight or the combination of abacavir and ethanol, with a washout period of seven days between treatment. Concomitant administration of ethanol and abacavir resulted in a statistically significant 41 percent increase in abacavir AUC; no changes in ethanol blood concentrations were observed. The increase in abacavir AUC is unlikely to be clinically significant, as the levels were within the ranges observed in previous pharmacokinetic studies of abacavir which employed higher abacavir doses and did not demonstrate additional safety issues [156].

Acute administration of alcohol may increase plasma concentrations of other substrates by inhibiting isoforms such as CYP2D6 and 2C19 [157]. On the other hand, chronic administration may reduce plasma concentrations of drugs metabolized by CYP2E1 and 3A [158;159]. Thus, there is potential for induction of PI and NNRTI metabolism with chronic alcohol use. Such an interaction may result in subtherapeutic levels of these agents, predisposing to resistance and compromising antiretroviral efficacy over time. However, there are currently no data documenting such an interaction. Appropriately conducted pharmacokinetic studies are necessary to confirm the existence of an interaction between antiretrovirals and chronic alcohol use, and to clarify appropriate management strategies.

## Sildenafil (Viagra)

Recently, several cross-sectional studies have been published describing the use of sildenafil as a recreational agent by gay and bisexual men at raves and circuit parties [160;161]. Within this context, sildenafil is often used to counter the effects of other recreational drugs on sexual performance. Since sildenafil is a substrate of CYP3A4, significant potential exists for sildenafil associated toxicity as a result of PI mediated inhibition of this isoenzyme [162]. Several small pharmacokinetic studies examining combined sildenafil-PI administration support the possibility of a potentially dangerous interaction. In one study, the addition of a single 25 mg dose of sildenafil to six HIV-positive patients receiving indinavir based antiretroviral therapy resulted in plasma concentrations of sildenafil that were 4.4 times that of dose-normalized data extracted from the literature [163]. All patients in the study reported adverse effects associated with sildenafil, including flushing and rhinitis. In addition, the mean maximal decrease in blood pressure noted was 14/10 mm Hg, which is greater than that reported following a single dose of 100 mg of sildenafil. Similarly, in two separate, randomized, open label, pharmaco-

kinetic studies, the AUC of sildenafil increased 2.4 and 11 times by concomitant saquinavir and ritonavir, respectively, relative to placebo [164]. The effect of this interaction may be magnified further since sildenafil is often used in conjunction with amyl and butyl nitrates (poppers), the combination of which may predispose patients to life-threatening hypotension and cardiac complications. Given these data, clinicians should advise their patients to not exceed 25 mg of sildenafil in a 48 hour period when taking concomitant PI-based therapy.

Other agents in this class, including vardenafil and tadalafil, are also CYP<sub>3A4</sub> substrates, and are thus prone to similar interactions with protease inhibitors. Dosage reductions are also recommended when coadministering these products with PI-based therapy.

## Guidelines on Managing Potential Drug Interactions

Since new therapeutic agents are continually emerging, it is virtually impossible to maintain a current, all-inclusive database of every potential drug interaction that may be encountered. When data are lacking regarding a particular drug combination, familiarity with the basic pharmacokinetic and pharmacodynamic characteristics of the involved agents may help practitioners predict the likelihood of possible interactions.

Once it has been identified that a patient may be at risk of experiencing clinically significant consequences (i.e., decreased therapeutic efficacy or increased drug toxicity) of a potential interaction, management options will depend upon a number of factors. The mechanism and clinical consequences of the interaction, timing of drug coadministration, availability of therapeutic alternatives, and patient convenience need to be considered.

In the context of recreational drugs, the most clinically relevant and significant interactions of concern are those involving dangerous elevations of psychoactive drug levels by protease inhibitors. For agents used to treat opiate dependence (e.g., methadone, buprenorphine), interactions with antiretrovirals may precipitate symptoms of toxicity or withdrawal.

Metabolic interactions may often be managed by adjusting drug dosages and/or dosing intervals, or substituting one agent for another with a different enzymatic profile. Although one method of avoiding a potential interaction between a recreational agent and an antiretroviral would be to temporarily discontinue HAART during the time that the recreational drug is used, this is not an acceptable solution due to the need to maintain exceptionally high (i.e., greater than 95 percent) adherence to HAART in order to optimize viral suppression and prevent viral resistance.

A more reasonable approach may be to modify either an individual's drug use or alter his or her HAART regimen. For instance, it may be desirable to avoid prescribing ritonavir-containing regimens to persons who regularly use MDMA, or avoid NNRTIs in subjects stabilized on methadone maintenance therapy. However, this is often not possible, since the majority of first-line protease inhibitors need to be boosted by ritonavir for optimal effects, and NNRTIs need to be avoided in some patient populations, such as those at risk of hepatotoxicity. Individual viral resistance patterns may also limit flexibility in antiretroviral prescribing.

Therefore, an alternative solution is to encourage individuals to modify drug use behavior. For example, persons using club drugs may be advised to be aware of the risks of adulterated drugs, to use small doses (e.g., one-half or one-quarter of what they might normally take), to wait at least 2 hours between doses, to avoid alcohol, to replenish fluids and sodium regularly, and to take frequent breaks from dancing. Individuals should be counseled on the signs and symptoms of drug toxicity and advised to seek immediate medical attention if these occur.

## Conclusion

The increasing numbers of available PIs and NNRTIs as well as newer classes of antiretrovirals, and the identification of various isoforms of the cytochrome P450 enzyme system and other drug transporters have heightened awareness about the significance of drug interactions in the HIV population. However, recreational drugs are often not considered by both clinicians and patients when reviewing a particular medication regimen for potential interactions. One of the inherent concerns associated with recreational drug use is that the margin of safety for many of these substances is often poorly defined, and quality control is often highly variable. Thus, factors which may lead to unpredictable drug concentrations can further increase the risk of adverse outcome. Given the rising incidence of HIV infection among substance users and the increasing use of complex combination antiretroviral regimens, the risk of adverse drug interactions with possibly fatal consequences cannot be overlooked or ignored. Clinicians should therefore strive to gather information about prescription, nonprescription, recreational, and illicit drug use as part of a comprehensive medication history. Reassuring the patient that confidentiality will be respected and the use of open-ended questions directed in a nonthreatening and nonjudgmental manner will facilitate the information gathering process. Appropriate counselling and management strategies may minimize the risk of potentially serious adverse outcomes.

Much of the information presented in this chapter is largely extrapolated from in vitro pharmacokinetic experiments, case reports or animal model studies. There are obviously many limitations in applying such data to clinical practice settings. With case reports, information is often anecdotal in nature. Patients' own recall bias is an obvious limitation, making direct causality difficult to establish. Even when in vitro or in vivo data are available, results often may not be directly extrapolated to clinical situations. For instance, much of the interaction information for ritonavir is based on full dose (i.e., 600 mg BID) studies. However, ritonavir is now frequently used at lower doses (e.g., 100–200 mg QD or BID) as a pharmacokinetic boosting agent. Ritonavir can inhibit CYP450 activity and increase protease trough concentrations in a dose-related manner [165]. Therefore, the frequency, extent, and/or clinical significance of interactions with ritonavir 100 mg BID may be lower compared to higher doses of ritonavir. As an example, when efavirenz was added to a combination of amprenavir 600 mg twice daily plus ritonavir 100 mg twice daily, amprenavir concentrations were decreased by almost 80 percent; however, when the ritonavir dose was increased to 200 mg BID, amprenavir levels remained stable in the presence of efavirenz [166]. Furthermore, great variability exists between individuals in their responses to drugs, including recreational agents. Therefore, a combination that might lead to toxicity in one person may be well-tolerated without consequence by another.

These confounding factors highlight the importance of designing interaction studies that accurately reflect situations encountered in clinical practice. Such information is urgently needed in order to optimize HAART-associated outcomes in this segment of the HIV-infected population. Existing data may serve as a tool for clinicians in anticipating, and hopefully averting, potential detrimental interactions with recreational drugs.

## **Snapshot: Heads in the Sand—How Pharmaceutical Research Practices Deny HIV-Positive Drug Users Life Saving Information**

*Mauro Guarinieri and Tracy Swan\**

The standard of care for HIV disease has evolved through years of research, yet HIV-positive drug users have received fewer benefits from such research than non-users. Research on interactions between antiretroviral agents and illicit drugs is a particularly neglected area, due to the collective refusal of antiretroviral manufacturers to conduct studies with illegal substances, or issue warnings based on available data.

### **Interaction between Antiretroviral Agents and Recreational Drugs**

According to UN researchers, “Interactions between agents commonly prescribed for patients with HIV and recreational drugs can occur, and may be associated with serious clinical consequences. Clinicians should encourage open dialogue with their patients on this topic.”[1].

One of these interactions, overdose, is a horrific—and needless—consequence of the paucity of research into drug-drug interactions. The first formally reported death due to interaction between an antiretroviral and an illicit drug, MDMA (3–4 methylenedioxymethamphetamine, commonly known as “ecstasy,” or “X”), was recorded in 1996. A coroner’s report confirmed that Phillip Kay, who was taking a combination of antiretroviral agents that included ritonavir (an extremely potent metabolic inhibitor marketed as an HIV protease inhibitor called Norvir), died from an MDMA overdose. Although Kay’s partner, Jim Lumb, was sure that Phillip had taken no more than 2.2 MDMA tablets, the coroner reported that Kay had the equivalent of 22 tablets in his bloodstream at the time of his death [2].

Since Phillip had used ecstasy tablets with no ill effects a few weeks prior to starting ART, Lumb suspected that Kay’s death might have been caused by an interaction and contacted Abbott, the company that markets Norvir. “I felt that if an interaction existed,” said Lumb, “the best way to warn patients was at the

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point of prescription—perhaps on the patient info sheet—rather than leaving it to chance by leaving it to word-of-mouth or dependent on the user having read this or that magazine.”[2].

P. Kon, a senior medical advisor from Abbott Laboratories, said that the company had assessed a “theoretical” interaction, and concluded that ritonavir could inhibit the metabolic pathway and create “a two to threefold increase” in MDMA levels; poor metabolizers, however, could experience an increase “as high as five to tenfold.” Abbott had not investigated interactions between ritonavir and MDMA or any other recreational drug because they view recreational drugs as never safe to use and will not condone their use under any circumstances [2;3].

Instead of issuing a warning, Abbott created a fact sheet for British doctors that was only available upon request. The company chose not to announce the ritonavir-MDMA interaction, “for fear that this would be construed as an endorsement of the use of illegal drugs.” According to Lumb, the coroner agreed that Abbott should include a clear and specific warning on the interaction between ritonavir and MDMA on the drug’s packaging, instead of withholding information because of concerns about encouraging illegal use [2;3].

Fatal and near-fatal interactions have continued to occur. In 1999, Harrington and colleagues reported a life-threatening interaction with MDMA and gamma-hydroxybutyrate (GHB) in an HIV-positive individual treated with a combination that included two protease inhibitors (ritonavir and saquinavir). Initially, this individual experienced an unusually prolonged effect after a small dose of MDMA, and, subsequently, a “nearly fatal reaction” from a small dose of GHB [4].

In 2000, Hales and colleagues reported a potentially fatal interaction between methamphetamine and ritonavir following the death of an HIV-positive Australian man. The report found that there was a

[r]easonable basis for proposing that interaction(s) between the metabolic pathways of HIV protease inhibitors and the known recreational drugs may have contributed to this person’s death. It is therefore suggested that patients who are prescribed protease inhibitor drugs are made aware of the potential risks of using any form of recreational drugs metabolized by CYP2D6, particularly methamphetamine. [5].

As of September 2005, Norvir's patient information insert still did not mention a potential interaction between MDMA or methamphetamine. Instead, it simply and vaguely told consumers that "Norvir may interact with other medicines, including those you take without a prescription. You must tell your doctor about all of the medications you are taking or planning to take." [6].

The corresponding prescribing information, mainly intended for physicians, does not mention an interaction with MDMA. The label does mention methamphetamine, which is also manufactured by Abbott as Desoxyn. It appears in a table titled, "Drugs in which Plasma Concentrations May Be Increased by Co-Administration of Norvir," but no additional information is provided [6].

Aside from overdose, additional potential consequences of drug-drug interactions include:

- ▶ decreased levels of illicit drugs, methadone, and buprenorphine, resulting in withdrawal symptoms;
- ▶ increased levels of ARVs, with corresponding increases in toxicity that may lead to discontinuation of therapy;
- ▶ decreased levels of ARVs to subtherapeutic levels;
- ▶ and development of resistance, which compromises treatment efficacy and may limit future options (this is of particular concern in many resource-poor settings, where few second-line options are currently provided).

### **Paucity of Interaction Data: Rationale and Opportunities**

The pharmaceutical industry has consistently refused to perform adequate studies or disseminate the scant data available on interactions between antiretroviral agents and illicit drugs. Since these interactions can have fatal consequences for HIV-positive people who use drugs as well as antiretrovirals, the industry's refusal to investigate interactions between illicit drugs and antiretroviral agents or to promulgate information about known or suspected interactions on the grounds that these actions condone drug use cannot be justified.

In addition to not wanting to appear to be supporting drug use, the pharmaceutical industry also uses legal grounds to justify its refusal to investigate drug-drug interactions. Yet provisions in the United Nations' two primary drug

control treaties—the 1961 *Single Convention on Narcotic Drugs*, and the 1971 *Convention on Psychotropic Substances*—provide a loophole for research involving illicit substances by limiting “...possession, use, trade in, distribution, import, export, manufacture and production of drugs exclusively to medical and scientific purposes.”[7]

There is precedent for medical and scientific research of illicit substances. Courageous sponsors and investigators have obtained approval from regulatory bodies, although these trials are subject to political pressure. The Multidisciplinary Association for Psychedelic Studies (MAPS) sponsored a U.S. trial of MDMA-assisted Psychotherapy in the Treatment of Post Traumatic Stress Disorder (PTSD). The trial was approved by the Food and Drug Administration in 2001, and the U.S. Drug Enforcement Agency granted a Schedule I license to the Principal Investigator in 2004. The trial is now underway. Another MAPS-sponsored investigation of MDMA for use in treating PTSD was launched in Spain, but did not fare as well. Despite the Ministry of Health’s permission, the study was shut down by pressure from Madrid’s drug enforcement agency.

Companies have also cited concerns about variations in strength, purity, and dosing of street drugs as an insurmountable barrier to conducting interaction studies. However, there are numerous opportunities to characterize purity of illicit substances. On-site MDMA testing for users has been approved by the Dutch government and the city of Vienna (when performed by a scientific institution); subsidized by the French federal government; made available in some parts of Germany upon agreement with local legal authorities; and allowed in Bern, Switzerland, and Barcelona, Spain, where it is supported by local and federal legal authorities [8]. For many years, Switzerland has provided heroin assisted treatment, which substitutes pharmaceutical heroin for illegal heroin. In the United Kingdom, prescription heroin has been available for decades. Additionally, current and future research on heroin substitution in other countries, and HIV cohorts enrolling IDUs, such as the Swiss HIV Cohort, may offer opportunities to investigate potential interactions between antiretroviral agents, heroin, and other substances.

Although consistent dosing is a germane concern, many pharmacokinetic (PK) studies have investigated potential interactions between antiretroviral agents and medications used to treat anxiety, pain, and serious psychiatric conditions. These medications are often used in combination, rarely at a uniform dose, and

are sometimes used illicitly. Neither these PK studies nor their results have been invalidated on the basis that patients use these drugs at varying doses.

A case in point comes from the United States, where Abrams and colleagues investigated potential pharmacokinetic interactions between cannabinoids (using both marijuana and dronabinol, an orally-administered synthetic form of the main psychoactive component of marijuana) and two protease inhibitors, nelfinavir and indinavir [9;10]. This study did not examine differences in potency among every available variety of marijuana, nor every possible dose, yet it produced results that are clinically relevant to an increasing number of HIV-positive marijuana or dronabinol users.

### **Addressing the Problem**

In 1999, experts participating in the “Interactions between Drugs of Abuse and Pharmacotherapeutic Agents Used in the Treatment of AIDS and Drug Addiction” workshop convened by the National Institute on Drug Abuse (NIDA) addressed the lack of research on drug-drug interactions by producing the following recommendations:

- ▶ Study the underlying mechanisms of drug interactions and metabolic pathways
- ▶ Support compound synthesis, including conjugates with collaborations from NIAID and FDA
- ▶ Develop and validate *in vitro/in vivo* models to study drug-drug interactions
- ▶ Conduct exploratory clinical pharmacology and diagnostic screening studies
- ▶ Study factors and mechanisms of drug induction
- ▶ Study interactions between illicit drugs (cocaine, marijuana, heroin) and licit drugs such as alcohol, cigarettes, and non-prescription and prescription drugs including anti-infective or antipsychotic drugs (some of which are used in the treatment of comorbid disorders)
- ▶ Organize clinical trials networks to study drug-drug interactions

- ▶ Study methodological issues in conducting drug-drug interactions studies
- ▶ Study pharmacodynamics of drugs and the effect of interactions on their therapeutic efficacy
- ▶ Conduct observation studies of interactions with current drugs among subjects in treatment
- ▶ Study drug interactions among drugs currently in development
- ▶ Develop protocols for the clinical management of drug interactions
- ▶ Design clinical trials in special populations that may need simplified protocols
- ▶ Develop and/or refine methods of drug detection
- ▶ Study genetic factors in drug-drug interactions
- ▶ Support the training of clinicians/scientists to study and manage drug interactions [11].

These recommendations have been largely ignored over the seven years since they were issued. In the meantime, hundreds of HIV-positive drug users are forced to conduct uncontrolled, one-person experiments, often on a daily basis.

Without an evidence base, or clear labeling of antiretroviral agents about lack of data on concomitant use with street drugs, legions of HIV-positive drug users and clinicians, community health care workers, and treatment educators are forced to rely upon anecdotal and case reports, and informed guesswork based on knowledge of metabolic pathways and in vitro—rather than in vivo—studies. The lack of data denies HIV-positive drug users the agency to make decisions that could save their lives.

It is past time for stakeholders to turn up the heat by urging that NIDA's recommendations be fully supported. We must insist that regulatory authorities in the United States and Europe require more comprehensive information on interactions between antiretroviral agents and illicit drugs prior to their approval, and that interaction study results be included on antiretroviral drug labeling, regardless of whether a substance is classified as legal or illegal.

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The co-occurrence of alcohol misuse disorders and HIV infection is common. For those IDUs who are coinfecting with HIV and Hepatitis C, alcohol treatment is critical, as ongoing alcohol use has been shown to accelerate the progression of liver damage.

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# Managing Alcohol Misuse Disorders in HIV and Hepatitis Infected Patients

Jon Levenson and Jay Dobkin\*

Alcohol misuse disorders are major and under-appreciated sources of medical as well as psychosocial difficulty in injection drug users (IDUs). Alcohol adds an entire range of potential neuropsychiatric disorders as well as increasing the risk of medical complications such as pancreatitis, cardiomyopathy, aspiration pneumonia, and trauma. In addition, alcohol abuse has added significance for individuals infected with hepatitis C virus (HCV) and especially those coinfecting with HIV since alcohol substantially increases the progression rate of liver damage. Beyond this, the spectrum of alcohol misuse often leads to psychosocial complications that can destabilize adherence to antiretroviral

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therapy. This chapter focuses on those aspects of alcoholism that have a special impact on injection drug users infected with HIV.

## Epidemiology of Alcohol Disorders

Alcohol misuse disorders (abuse and dependence) are quite prevalent in general populations. Epidemiologic studies reveal that lifetime prevalence rates are 17 percent for men and 10 percent for women between the ages of 18 and 44 (Regier 1988). Similarly, six month rates are 6 percent for men and 3 percent for women in this same age range. Those with active alcohol misuse are at increased risk of becoming infected with HIV; several reports have found that alcohol-dependent patients may have an infection rate of 10 percent or greater [Mahler 1994]. Most of these patients had comorbid nonalcohol substance misuse, and when investigators have looked at a purer sample of alcoholic patients, infection rates are somewhat lower (8.7 percent) [Schleifer 1996].

While rates of alcohol abuse and dependence in HIV-infected populations have not been studied as rigorously, investigators have found lifetime alcoholism prevalence rates ranging from as high as 30 percent to 60 percent [Dew 1997]. Current alcohol misuse in HIV-infected populations also has a significant range, depending on the specifics of the population. One study found that HIV-infected military personnel had a rate of 3.6 percent alcohol misuse [Brown 1992], while another found a prevalence rate of 11.6 percent of current alcohol misuse in a more typical infectious diseases clinic population [Dew 1997]. Thus, the co-occurrence of alcohol misuse disorders and HIV infection is common. Possible explanations for this co-occurrence include behavioral disinhibition resulting from alcohol intoxication which may lead to unsafe sexual and injection drug use practices, as well as to having multiple sexual partners; also, lifetime prevalence of injection drug use, a leading risk factor for HIV, is increased in alcoholic patients. Mood disorders such as major depression are frequent in HIV-positive alcohol abusers, and depression itself is associated with poor self care, low locus of control, and poor impulse control [Kelly 1993].

## Neuropsychiatric Disturbances Associated with Alcoholism

Clinicians need to be aware of common withdrawal syndromes that are associated with abrupt alcohol cessation. Such states are often encountered in the acute hospital setting when patients are admitted for urgent medical care but can also be seen in outpatient

settings. Withdrawal syndromes include uncomplicated alcohol withdrawal, withdrawal seizures, delirium tremens, alcoholic hallucinosis, and Wernicke's encephalopathy.

Evaluation of withdrawal includes careful and early assessment of alcohol use, history of past withdrawal, type of alcohol used and its potency, amount ingested on daily basis, and date and time of last drink taken. Management involves an ongoing dosing schedule of a benzodiazepine such as chlordiazepoxide with assiduous and frequent assessments to monitor the patient's status and clinical response to this regimen. All patients should also be prescribed thiamine 100 mg qd, folic acid, and a multivitamin. The Clinical Institute Withdrawal Assessment for Alcohol-revised, or CIWA-AR [Sullivan 1991], is a useful instrument in helping the clinician evaluate the therapeutic response of a detoxification regimen. Wernicke's encephalopathy (WE) is an acute deficiency of thiamine and presents with overt delirium. It is managed with intravenous thiamine loading and magnesium sulfate prior to glucose loading. If WE is not diagnosed and promptly treated, it can lead to a chronic amnestic syndrome known as Korsakoff's dementia.

Delirium tremens (DT) is a life-threatening and florid withdrawal state that presents with an agitated delirium; signs and symptoms include disorientation, psychomotor agitation, paranoia, perceptual disturbances (most often visual hallucinations or illusions), and autonomic instability (tachycardia, sweating, fever) and tremor. DT is best managed if it is recognized early and quickly treated with benzodiazepines and supportive care. Initial goals of treatment include vital sign stabilization and a mildly sedated state. It is usually advisable for patients to have a private room for decreased stimulation, and a staff member for constant observation is often necessary. While benzodiazepines are still considered the standard of care to manage withdrawal, other treatments are being actively studied with anticonvulsants such as valproic acid and gabapentin yielding some promising results [Myrick 2001]. Unlike deliria from toxic-metabolic or systemic etiologies, the electroencephalogram in DT shows a rapid brain wave pattern. This distinction can help differentiate DT from other deliria when the etiology of an acute confusional state is unclear.

## Assessment of Alcohol Dependence

Once patients have completed a detoxification regimen to prevent or treat withdrawal, definitive assessment and treatment of the underlying alcohol disorder commences. Two screening instruments that are utilized are the CAGE questionnaire and the Michigan Alcoholism Screening Test. Screening for alcohol disorders should be done routinely in all HIV-positive patients, starting with the patient's initial visit and then continuing on regular basis (such as annually), even if an initial screen was negative. For patients who

screen positive for problem drinking, a more formal assessment to make the appropriate alcohol diagnosis needs to be pursued. Diagnoses range from episodic problematic or dangerous drinking, which may not meet criteria for a formal DSM-IV disorder, to overt alcohol abuse or dependence. These latter diagnoses can be active, or patients may have a disorder in remission. A nonjudgmental and empathic approach with open ended questions will result in the most candid answers about alcohol use. Specific questions are also helpful, such as “when was your last drink of alcohol, even just one?”

As alcoholic patients rarely admit to having a serious problem, the first order of business, once the diagnosis is made, is to communicate the need for treatment and to persuade the patient to proceed. When patients deny or minimize their need to address alcohol dependence, an intervention such as a therapeutic confrontation, may be indicated to help overcome resistance and denial. In this strategy, loved ones are included as well as professional staff, and the goal is for the patient to agree to pursue a recovery program. Both at this initial juncture as well as during relapses, motivational interviewing is an important technique to assess an individual’s readiness for treatment. Such interviews can help patients confront their denial of the severity of their alcoholism, and to begin to accept responsibility for making the necessary changes to overcome and cope with their disorder [Miller 2003].

For those IDUs who are coinfecting with HIV and Hepatitis C, alcohol treatment is critical, as ongoing alcohol use has been shown to accelerate the progression of liver damage. While it is unclear if there is a certain threshold amount of ingested alcohol below which alcohol use in moderation may not have deleterious effects on the liver in this population, the goal should always be sustained abstinence since controlled drinking, for patients with a history of problematic drinking, is seldom successfully achieved. Cytokine treatment of Hepatitis C infection with alpha interferon may cause neuropsychiatric complications such as depression and agitation which may lead to a relapse of alcohol abuse as an attempt to self-medicate these distressing emotional symptoms. Emerging data suggest that patients at high risk for depression should be considered for prophylactic treatment of depression before interferon therapy is started with standard selective serotonin receptor inhibitors [Musselman 2001].

Alcohol use can also have a potent negative effect on adherence to antiretroviral therapy (ART). While it is clear that overt alcohol abuse or dependence often leads to destabilization of a person’s life with progressive downward decline and inability to care for self, including adherence to ART, it is also important to emphasize that even problematic drinking limited to occasional binges can have negative effects on adherence, as both clinical research as well as clinical management suggest that ART adherence needs to approximate 100 percent to maintain durable viral suppression. Thus any evaluation of alcohol use must determine if the drinking episodes, or their aftermath, have any negative effects, direct or indirect, on adherence to ART.

Alcohol use is also associated with risky sexual behaviors as it affects judgment and impulse control and the likelihood of employing safer sexual practices is lower. Alcohol may also prompt patients to have sex with more partners and with people who they do not know or are not well acquainted with. For HIV-infected IDUs, risky sexual practices can lead to superinfection with resistant strains of HIV, as well as other sexually transmitted diseases [Kelly 1993]. Communicating both serostatus as well as discussing safer sexual practices prior to sexual activity is a key strategy to reducing HIV transmission, but this is rarely done in persons who are actively drinking prior to having sex. It is important for the clinician to inquire regularly about alcohol use and unsafe sexual practices. This query should be done in a supportive way so that a patient feels comfortable enough to disclose the specifics of these behaviors. Getting candid answers will help patient and care provider formulate a treatment plan to reduce or stop risky behaviors, or in the case of ongoing risky behaviors, a new plan can be discussed and instituted.

## Treatment of Alcohol Dependence

Treatment of alcohol dependence initially includes referral to a specific alcohol program, such as a three or four week inpatient rehabilitation stay, or a day program that patients would attend several days a week. All patients with an alcohol disorder should be referred to a Twelve Step program such as Alcoholics Anonymous (AA) which is a self-help group that emphasizes acceptance of a dependence on alcohol, provides mutual support and understanding of how this disorder has adversely affected one's life trajectory, and connects the alcoholic patient to a healthy community of those in recovery. AA espouses a model of complete abstinence from alcohol use and is not supportive of those who attempt to continue to drink in a more moderate way. In addition to recovery programs, treatment of alcoholism may include some form of psychotherapy, such as individual or couples therapy.

### **Pharmacotherapies for alcohol use disorders**

Pharmacotherapies such as disulfiram, naltrexone, and acamprosate may be helpful adjunctive treatments to maintaining abstinence from alcohol and are most successful in patients who are actively engaged in psychosocial therapies. In addition to these treatments, antidepressant, antipsychotic, anti-anxiety, and mood stabilizing medicines are increasingly used in the treatment of patients who may have other psychiatric comorbidities such as mood, anxiety, and psychotic disorders.

Disulfiram inhibits alcohol dehydrogenase and thus causes an accumulation of the aldehyde state of alcohol. It works as a deterrent to any alcohol use; if alcohol is con-

sumed with disulfiram, a toxic reaction typically occurs in which flushing, nausea and vomiting, and severe headache develop. Disulfiram is an effective treatment in patients who are motivated to take it daily and thus who express strong interest in staying sober. It is not initiated in the inpatient setting as patients typically express ambivalence during the early stages of their attempts at sobriety. Disulfiram is contraindicated in severe liver disease. Relevant drug interactions include raising blood levels of phenytoin and isoniazid. Disulfiram is contraindicated with alcohol-based liquid preparations of some HIV protease inhibitors including amprenavir and ritonavir-lopinavir oral solutions as well as ritonavir oral solution and capsules.

Naltrexone is an oral opioid antagonist that is a treatment for opiate abuse disorders; it has also been used in alcoholism as it appears to block the euphoriating and pleasurable effects of alcohol. Some have advocated that use of naltrexone may convert a problematic drinker into a controlled drinker though this has not been systematically studied. Because it is an opioid blocker, it cannot be used with those who take opioid analgesics for pain management or are on opiate substitution therapy. It also has potential hepatic toxicity and needs to be used with caution in liver disease. Oral dosing starts at 25 mg daily with gradual increase to 50 mg daily. As naltrexone is used as a treatment of opioid dependence in IDUs, naltrexone may benefit patients with both alcohol and opioid addiction. A new monthly injectable long-acting preparation of naltrexone is expected to be released in 2006 or 2007.

Acamprostate is a novel treatment for alcoholism that has efficacy in clinical trials prolonging length of abstinence. While its mechanism of action is not fully understood, it is a glutamate receptor modulator, and chronic alcohol abuse is known to disrupt several neurotransmitters, including glutamate. Its therapeutic effect is to reduce craving for alcohol. It can be used in liver disease; the only absolute contraindication is severe renal impairment. The starting and maintenance dose is 666 mg TID; side effects include diarrhea. Because of its TID dosing, this treatment requires good adherence as well as social support. There have been anecdotal reports of combining acamprostate with naltrexone to optimize alcohol pharmacotherapy by employing two medicines with different mechanisms of action.

Since nonsubstance use psychiatric comorbidity is prevalent in alcohol dependent people, the clinician needs to closely monitor for the presence or even emergence of mood, anxiety, and psychotic disorders once a patient is sober and in alcohol treatment. Unipolar depression warrants aggressive antidepressant treatment as well as psychotherapy, and bipolar spectrum disorders are treated with mood stabilizing agents such as lithium, valproate, as well as atypical antipsychotics such as quetiapine, olanzapine, risperidone, and others. Drug interactions can be problematic so it is essential that all interactions are considered prior to starting treatment; this is also important if changes are made to an ART regimen. First line treatment for anxiety

disorders such as panic disorder and generalized anxiety disorder includes selective serotonin reuptake inhibitors such as citalopram and escitalopram as well as serotonin-norepinephrine reuptake inhibitors (venlafaxine). These drugs have minimal drug interactions with ART regimens. Benzodiazepines are in general contraindicated in this population as the risk of both abuse and dependence is high, and the risk for harm from combined use of alcohol and benzodiazepines, or overdose is also elevated. Both atypical antipsychotics as well as the older typical class are also often employed to treat anxiety disorders in those who do not respond to SSRIs or SNRIs. While extrapyramidal side effects are less common with the newer atypical agents, other side effects such as metabolic syndrome with weight gain and glucose dysregulation can be seen. The treatment of psychotic disorders such as schizophrenia, schizoaffective disorder, and mood disorders with psychotic features is beyond the scope of this chapter. However, it is important to assess for presence of hallucinations, delusions, and disordered thought process as psychotic patients often have alcohol use disorders as well [Schuckit 1997; Cantor-Graae 2001].

Rates of attempted and successful suicides are alarmingly high in alcohol abuse and dependence and thus careful assessment and ongoing monitoring is critical. Patients may require emergent inpatient psychiatric hospitalization for safety, evaluation, and treatment. Alcohol detoxification as discussed above is often accomplished at an inpatient psychiatric unit unless life-threatening withdrawal, such as delirium tremens, is present or suspected. Once the patient is psychiatrically stable, transfer to an inpatient alcohol rehabilitation center may be indicated. In less severe cases, patients may transition to a structured day program.

## Alcohol-Related Liver Disease

Alcohol ingestion leads to a range of liver pathology from asymptomatic fatty liver to cirrhosis and liver failure. Heavy intake (>80g/day) for more than 10 years seems to be the threshold for severe liver disease [Lelbach 1975], although short term exposure to large amounts can produce fatty liver or alcoholic hepatitis. Since at least half of those in the heaviest alcohol ingestion category do not progress to end-stage disease other factors have been sought. Among the important cofactors, gender and hepatitis virus infection stand out. Perhaps because they metabolize alcohol at a slower rate, women seem to progress to advanced stages of alcoholic liver disease at a higher frequency and more quickly than men [Gavaler 1995].

Diagnosis of alcoholic liver disease may be difficult until the end-stage complications ensue. Patients may be asymptomatic and have unremarkable physical examina-

tions even with advanced disease. Alcoholic hepatitis may present with signs of fever, abdominal pain, and tenderness. Cirrhosis can feature evidence of portal hypertension such as splenomegaly, ascites, and caput medusa or signs of hepatic failure including palmar erythema, gynecomastia, and hepatic encephalopathy. Liver function tests are often abnormal; a common pattern includes an increase in AST (SGOT) that exceeds the increase in ALT (SGPT) by twofold. Hematologic abnormalities such as leukocytosis, macrocytosis, and thrombocytopenia are often identified in those with alcohol-related liver disease.

### **Alcohol and viral hepatitis**

Hepatitis B and C infection are highly prevalent among HIV-infected IDUs and HIV appears to significantly accelerate the course of HCV disease leading to end stage liver disease, cirrhosis, and hepatocellular carcinoma. Since treatment of HCV is difficult, expensive, and has limited efficacy in HIV-positive patients, especially those infected with genotype 1, it is important to understand cofactors that may worsen the course and intervene in those that are reversible. Among the factors known to worsen the course of HCV infection, only heavy alcohol consumption appears modifiable. Other risk factors include male gender and older age at the time of infection [Poynard 1997].

Alcohol ingestion worsens the course of HCV infection in at least three important ways: 1) it accelerates the progression of liver fibrosis and the risk of developing cirrhosis; 2) it increases the risk of hepatocellular carcinoma; and 3) it decreases the response to interferon therapy. In a cohort of injection drug users with HCV there was a 3.6-fold increase in relative incidence of end stage liver disease in those consuming >260g/week of alcohol [Thomas et al. 2000]. Some studies have found that even limited alcohol intake may accelerate fibrosis in HCV infection [Pessione 1998] but this has not been clear in some others [Monto 2004]. Alcohol appears to exert a potent synergistic effect with viral hepatitis on the risk of hepatocellular carcinoma. In an Italian study, the relative risk of hepatocellular carcinoma associated with surface antigen positive hepatitis B infection was 64.7 in alcoholics compared to 11.4 in non-alcoholics [Donato 1997]. A negative impact of previously heavy drinking on the response to alpha interferon treatment of HCV persisted even after achievement of abstinence [Okazaki 1994]. Many of these cofactors converge in the HIV-infected patient leading one group to estimate a median expected time to cirrhosis in a patient with less than 200 CD4 cells who drinks more than 50 g of alcohol daily of 16 years versus 36 years for a comparable HIV-infected patient with more than 200 CD4 cells and 50 g or less of alcohol intake daily [Benhamou 1999]. The mechanisms by which alcohol aggravates HCV are not certain. Depression of cell mediated immunity may lead to an increase in the HCV replication rate and increase the range of HCV quasispecies. In addition alcohol may impair liver regeneration after injury.

## 4. Ethics, Clinical Research, and Drug User Involvement



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The first step to learning more about vulnerable groups' disease progression and response to drug therapies is simple: include the groups in trials. As it is, ARV agents are often marketed without accurate information appropriate for drug users, who comprise a large population of those who will receive the medications and interventions that researchers are investigating.

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## Clinical Trials and Active Drug Users: A Story of Unmet Needs

Konstantin Lezhentsev, Mauro Guarinieri, and Daniel Raymond\*

Most clinical trials are guided by research ethics that attempt to ensure that study participants are protected from exploitation and coercion, as well as other forms of harm. All clinical trials involve some degree of potential risk for the research subjects. Ethical research attempts to strike a balance between potential risks and benefits while protecting people from exposure to unreasonable dangers to their health and safety. The interpretation of these goals has led to standards and regulations that restrict or discourage research on groups perceived as vulnerable to exploitation or greater harm, such as prisoners and pregnant women.

Although the protection of research subjects remains an important concern, over time the debate on ethics has shifted away from excluding vulnerable persons' participa-

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tion in medical research in order to protect them from all risks. A growing number of researchers and advocates argue that such blanket exclusions may themselves be harmful by restricting the relevance and validity of research findings to narrowly-defined “ideal” study populations. According to these researchers and advocates, limiting research to “ideal” populations can result in an inadequate evidence base for understanding differences in the progression and manifestation of disease as well as the relative safety and efficacy of treatment in vulnerable groups.

Often, the impact of exclusion criteria in HIV research results in clinical trial study populations unrepresentative of the range of people living with HIV. For example, a recent analysis of eligibility criteria conducted by two large, government-funded clinical trials networks in the United States—the Adult AIDS Clinical Trials Group (AACTG) and the Community Programs for Clinical Research on AIDS (CPCRA)—analyzed the eligibility of participants in the separate Women’s Interagency HIV Study (WIHS) cohort of HIV-positive women. On average, at least 42 percent of women in the WIHS cohort would be excluded from AACTG and CPCRA studies.<sup>1</sup> This analysis was restricted to objective exclusion criteria, and could not determine the effects of criteria relying on investigator judgment, such as the following examples from AACTG and CPCRA protocols:

- ▶ Subjects considered by the investigator to be unlikely to comply with study treatment regimens or evaluation schedules, or likely to be harmed by active drug or alcohol use.
- ▶ Possible current substance abuse that could prevent compliance with the study medication, at the discretion of the local investigator.
- ▶ Patient should be able, in the clinician’s opinion, to comply with the protocol.

The first step to learning more about vulnerable groups’ disease progression and response to drug therapies is simple: include the groups in trials. The second and more complex step is to ensure that, when marginalized groups are included, they represent the full spectrum of the population targeted to receive the therapy. Although the ultimate goal of the process should be to learn how to prescribe drug therapy safely for the patient groups who will be receiving them, objective and subjective exclusion criteria often result in an inadequate evidence base for understanding differences in the progression and manifestation of disease as well as the relative safety and efficacy of treatment in vulnerable groups.

In HIV research, drug users and other socially stigmatized and marginalized individuals have historically been excluded from, or underrepresented in, clinical research. This lack of representation limits information on the comparative safety and efficacy of antiretroviral (ARV) treatments and hinders the development of optimal care for HIV-positive drug users. The marginalization of drug users in clinical trials also reinforces

the stereotypes and false assumptions used to justify the blanket or de facto exclusion of drug users from access to ARV treatment.

*Injection Drug Use and HIV/AIDS: Legal and Ethical Issues*,<sup>2</sup> a 1999 report by the Canadian HIV/AIDS Legal Network noted the following:

[t]o systematically exclude active drug users from clinical trials is equivalent to a refusal to obtain knowledge necessary to adequately treat those who are often most in need of care... [I]t is therefore ethically wrong to exclude these people from studies that can inform whether treatment for HIV-positive drug users needs to be adjusted from the treatment approaches used in people who do not use controlled substances.

Despite high HIV prevalence, drug users are still largely excluded from clinical trials, especially when the research applies to ARV treatment. According to Gerald Friedland, drug users have not been proportionally enrolled in most major North American and European trials. This includes studies conducted by the ACTG and CPCRA research groups.<sup>3</sup> As a result, ARV agents are often marketed without accurate information appropriate for drug users, who comprise a large population of those who will receive the medications and interventions that researchers are investigating. Under-studied areas relevant to clinical management include information on pharmacokinetic and drug-drug interactions between antiretrovirals and recreational drugs, complications of ARV therapy, prophylaxis of opportunistic infections, interactions with methadone and buprenorphine, and information on HIV disease itself.

Attempts to identify differences between HIV-positive injection drug users (IDUs) and non-IDUs in HIV disease progression, morbidity and mortality, and response to highly active antiretroviral therapy (HAART) have yielded mixed, often conflicting, results, due in part to methodological problems and a range of confounding factors.<sup>4</sup> Current and former IDUs living with HIV often experience significant non-HIV/AIDS-related mortality due to overdose, bacterial infections such as pneumonia, and violence. High rates of comorbidities, particularly hepatitis C coinfection and mental illness, have negative impacts on health and survival, and may compromise HIV treatment outcomes through decreased tolerability of HAART and poorer adherence.

While some studies have found poorer virologic and immunologic responses to HAART among IDUs, other research shows that injection drug users can clearly benefit from and adhere to HIV treatment at levels comparable to other groups, given proper adherence support and clinical management. Disparities in access to and engagement in health care related to stigma, discrimination, housing status, and incarceration may account for much of the reported differences in HIV treatment outcomes and mortality. In turn, HIV clinical guidelines specific to IDUs must incorporate adherence support, opioid substitution therapy, mental health screening and management, overdose preven-

tion, and hepatitis C care and treatment. A study comparing mortality in HIV-positive and HIV-negative IDUs in a large United States cohort underscores the importance of tailoring HIV care strategies to drug users to address broader health concerns.<sup>5</sup> The study indicated that HIV-positive injecting drug users initiating HAART at CD4 T cell counts above 350 experienced mortality rates comparable to HIV-negative IDUs. Early initiation of HAART, at a threshold higher than that recommended in clinical guidelines, yielded substantial reductions in non-HIV/AIDS-related deaths, most notably in deaths due to overdose and viral or bacterial infections. Earlier initiation of HAART has also been proposed for people coinfecting with hepatitis C, a group representing up to 90 percent of HIV-positive injection drug users.<sup>6</sup> Such research makes a compelling argument for broader inclusion of drug users in HIV clinical research to provide a better characterization of the relative benefits and risks of treatment in this population.

The Leadership Statement on Injecting Drug Use and HIV/AIDS,<sup>7</sup> a document presented at the XV International AIDS Conference in 2001, urged regulatory agencies to require pharmaceutical companies and other bodies to undertake clinically relevant trials involving active drug users. The same demand was raised by a massive international campaign that led to the inclusion of methadone and buprenorphine in the WHO model list of essential medicines. Both statements stressed the importance of securing informed and equal involvement of active drug-users in ongoing clinical trials of new anti-HIV agents. The statements identified this inclusion as part of a broader advocacy effort to provide full, equal, and universal access to ARV treatment for populations that had been discriminated against in receiving HIV treatment and prevention interventions.

Clinical trial enrollment criteria has shifted over the last decade from a blanket exclusion on people with “substance abuse” histories toward a focus on the discretion of individual investigators to determine whether a potential subject’s drug or alcohol use would limit their ability to fulfill the requirement of the study. Despite these changes, drug users are still often excluded from clinical trials because of concerns about adherence and loss to follow-up. In many respects, the current language and practices guiding trials have simply shifted the onus from trial sponsors to individual researchers.

The stereotype that drug users cannot adhere to HIV treatment remains the single most important factor limiting access to treatment for injecting drug users and, for the specific purpose of this chapter, their enrolment in clinical research. Studies by Ware et al.<sup>8</sup> outline the stereotypes of the non-adherent drug user as:

1. someone who leads a chaotic life;
2. someone who is constantly using drugs;
3. someone whose drug use automatically precludes them from taking medication as prescribed; and
4. someone whose life and problems are intrinsically different from non-users.

These widely-held assumptions contradict a wealth of evidence on adherence and drug users. While overall adherence rates among HIV-positive IDUs are lower in a number of studies, a substantial proportion of drug users demonstrate high levels of adherence to HAART. In addition, a range of interventions—including opioid substitution therapy, clinic- and community-based adherence support, treatment of mental illness, and housing—can increase adherence rates to levels approaching those of other groups of people living with HIV. The presumed inability of drug users to adhere to treatment results in beliefs that drug users are “difficult to treat” and poor candidates for HIV therapy.

These assumptions about adherence have also led to the practice of investigators excluding drug users from clinical research on the grounds that they are unable to adhere to complex treatment protocols and, therefore, also unable to participate in clinical research. The example of Thailand’s trial of the AIDSVAX gp-120-based vaccine, which involved 2,500 seronegative IDUs in Bangkok’s methadone clinics, refutes this widely held misconception. Retention in the cohort was remarkably high. Loss to follow up per year was reported at 1.5 percent,<sup>9</sup> while overall retention exceeded 90 percent during the three year study.

When these results are contrasted with Ware’s research into investigator bias regarding drug users’ capacity to adhere to treatment and their suitability for clinical trials, the focus for further advocacy is clear. The views and practices of researchers must be changed so that active drug users are seen as important and appropriate participants in clinical research. Clinicians are notoriously poor at predicting the likelihood that a patient will adhere to treatment, and often make erroneous assumptions of non-adherence based on patient characteristics including substance use and housing status.<sup>10–11</sup> Efforts to make clinicians better and more informed predictors of adherence should include the development and validation of simple screening tools to clinical trial exclusion criteria that rely on investigator discretion.

Without these kinds of changes, the research community will continue to fail in both investigating and addressing crucial issues regarding ARV treatment of HIV-positive drug users. Refusing to enrol active drug users in clinical research supports the reluctance, or unwillingness, of treating physicians to prescribe ARV to drug users. That such refusal is often based on researchers having their own stereotypes about drug use and drug users is clearly unacceptable. However, a better understanding of how investigators judge whether “active alcohol or substance use could compromise the subject’s safety or compliance with the study protocol procedures”—to cite representative language from current phase III protocols of investigational antiretrovirals—is key to developing effective advocacy for greater involvement of active drug users in clinical research.

Focussing on investigators, however, does not exclude the role of industry and government research sponsors. As rightly noted by Friedland,<sup>12</sup> there is not only a need

for more studies of HIV therapeutics among drug users, but also more studies on an array of abused substances, including prescribed and illicit drugs. When incorporating substance abusers into clinical trials, sufficient numbers should be obtained to enable stratification by substance abuse status. The overall clinical care of drug users during the trial should be improved by integrating medical, psychiatric, and substance abuse services, which, in turn, will bring more drug users into therapeutic trials.

All of these possibilities, however, will go unrealized if physicians continue to cling to the misconception that drug users are unable to adhere to ARV therapy. Until they reject this notion, they will keep overlooking the confounding factors that affect adherence and clinical outcomes. Like it or not, drug users represent a significant proportion of the global HIV-infected population. Yet stereotypes coupled with the variability of effects from illegal drugs and society's neglect and scorn toward drug users keep them locked out of ARV treatment research. Lack of research data then fuels and justifies physicians' refusals to prescribe ARV therapy for drug users.

It will require greater effort and cost to recruit hard-to-reach groups and keep them in clinical trials. But these steps must be taken and combined with creative strategies to help investigators work toward comprehensive representation of underrepresented groups in clinical research. One promising development is "network sampling," a system in which drug users work as peer recruiters and are proving to be more effective at reaching IDUs than professional community outreach workers.<sup>13</sup> Peer recruitment could be incorporated into clinical trials conducted in communities where large numbers of IDUs reside. In addition, researchers could consider seeking the advice and participation of community groups and local opinion leaders. Even if such efforts only result in the inclusion of a small number of active drug users in each clinical trial, the data can still be pooled using systematic reviews to provide better information to practitioners that may lead to safer prescribing.

It is time to break the vicious cycle of not including IDUs in research and then denying them ARV treatment because little data exists. Advocates and investigators who are truly concerned about public health must recognize that clinical research has to be relevant to the populations for whom the medications or interventions are intended. This simple principle can guide investigators in planning and conducting research on specific populations—including active drug users—that will support and develop the highest possible standards of treatment and care.

## **Snapshot: *Trials and Tribulations: Thai Drug Users and HIV Prevention Research***

*Karyn Kaplan\**

Thailand first documented an “explosive” HIV epidemic among injecting drug users (IDUs) in the late 1980s, when prevalence among incarcerated injectors skyrocketed from 2 percent to 43 percent within a six-month period. Since then, the lack of an effective government response has resulted in a persistent HIV epidemic of nearly 50 percent prevalence among injectors nationally. Between 2001 and 2004, there was still no decline in the IDU HIV infection rate, which remains at approximately 42.2 percent today.<sup>1</sup>

In response to the AIDS crisis among IDU, as well as the long history of human rights abuses against them, a group of Thai drug users organized the Thai Drug Users’ Network (TDN) in December 2002. Comprising over 100 HIV-positive and HIV-negative users from across the country, TDN works as an advocacy organization to bring attention and redress to the issues of HIV and human rights violations in their community. Most notably, TDN coordinated local and international coalitions to protest Prime Minister Thaksin Shinawatra’s violent 2003 drug war, which resulted in the extra-judicial execution of nearly 2,500 people allegedly involved with drugs. The drug war was notoriously characterized by a litany of other crimes including blacklists, arbitrary arrest and detention, forced drug treatment in makeshift military boot-camps, and the breach of due process.<sup>2</sup>

Against the backdrop of this repressive environment, Thai researchers began a clinical trial in 2005 studying the safety and efficacy of once-a-day Tenofovir (TDF), a drug currently used in HIV treatment, for pre-exposure prophylaxis (PREP) against HIV in injecting drug users.

TDN expressed support for the development of new HIV prevention tools for HIV-negative people, but criticized the lack of provision of a comprehensive prevention package for the trial’s 1,600 participants. It was clear that providing participants with clean injecting equipment—an evidence-based and cheap approach to IDU HIV prevention—was eminently more accessible than an expensive bio-medical intervention that was unlikely to reach Thai IDUs any time

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soon, even if proven effective. Yet according to the tenofovir PREP protocol, clean injecting equipment would not be distributed.

Through engagement and dialogue with the trial researchers and collaborating sponsors like the Ministry of Public Health and the U.S. Centers for Disease Control, TDN fought to ensure that basic ethical and procedural standards were respected, community representatives were involved in the protocol design and implementation, and that an acceptable standard of care and treatment was provided. Unfortunately, mutual agreement was never found on most of these points, and the trial began recruitment and implementation in 2005 without TDN's endorsement.

The tenofovir trial was not the first time that Thai IDUs have been used to benefit science. In 2003, more than 2,500 injectors were recruited into the AIDSVAX B/E HIV Vaccine Efficacy Trial by the Bangkok Metropolitan Authority (the vaccine was found to be ineffective, but principal investigator Kachit Choopanya, stated that "...Thailand has strengthened its research capacity and acquired valuable expertise with which to carry on clinical research").<sup>3</sup> The World Health Organization (WHO) has designated Thailand a target country for the development of a vaccine for primary HIV prevention because of this capacity, as well as the less-stated but obvious high infection rates among certain neglected groups, such as IDUs.

Given its enthusiasm and reputation for HIV research, it is surprising that the Thai government has repeatedly ignored scientific evidence supported by organizations such as WHO that shows that increasing the availability and utilization of sterile injecting equipment "contributes substantially to reductions in the rate of HIV transmission"<sup>4</sup> among IDUs. Active drug users are disproportionately affected by HIV yet have been excluded in Thailand from accessing anti-retroviral therapy (ART).<sup>5</sup> Currently, there are no government-sanctioned needle exchanges. Nor does Thailand promote harm reduction or comprehensive HIV prevention for IDUs as a matter of policy, despite the prime minister's pronouncement at the 2004 International AIDS Conference that "the government has changed its mindset and we now see drug users as patients who require our support and treatment."<sup>6</sup>

Since official rhetoric was not reflecting reality for IDUs in Thailand, TDN responded to the tenofovir trials by charging researchers

with exploiting injectors for their high HIV risk while providing a substandard prevention package to participants. Similar tenofovir PREP trials conducted in other countries among groups at-risk *sexually* for HIV provided participants with condoms along with counseling and other prevention interventions. Why was clean injecting equipment—the safety equivalent of condoms for groups at risk to HIV through drug use—not provided to IDUs? Why in Thailand were such safety standards not upheld?

Citing the Declaration of Helsinki—the World Medical Association’s guidelines for the ethical conduct of medical research in human subjects—TDN insisted that placebo-controlled trials (such as the Thai tenofovir PREP study) should only be used in the absence of proven prophylactic, diagnostic, and therapeutic methods. If a placebo trial was going to be implemented, clean injecting equipment must be provided. Trial investigators claimed that U.S. government policy prohibiting the use of federal funds to support needle exchange, as well as local Thai law, forbade them from providing a comprehensive prevention package. TDN countered that providing needles in the name of public health was not a crime according to the law, and that the Medecins Sans Frontieres–Belgium office in Bangkok was willing to act as a third-party provider. Yet investigators refused to alter their protocol. TDN also cited other flaws in the trial, including 1) lack of community involvement in the design of the protocol, 2) lack of a community advisory board, 3) potential for coercion of methadone clinic clients into the trial by methadone clinic staff who doubled as trial recruiters, and 4) sub-standard post-trial provisions of treatment and care.

TDN continued to challenge the trials by utilizing numerous avenues for advocacy including face-to-face and telephone dialogues and written correspondence. TDN also used the media, public letters, statements at conferences, public demonstrations, and participation in forums where researchers and community AIDS and human rights activists could gather and strategize about the issues raised by the tenofovir trials. Ultimately, TDN with allies including the Center for AIDS Rights and the Thai Network of People Living with HIV/AIDS brought a petition to the National Human Rights Commission (NHRC) to investigate the trial’s possible ethical and human rights breaches. The coalition was immediately confronted with the challenge of replacing the commissioner assigned to the case, who also sat on the institutional review board committee that approved the tenofovir trial. In a meeting prior to TDN’s request for

his resignation from the case due to his conflict of interest, the commissioner addressed drug users by saying, “Why can’t you give a little back (to the Bangkok Metropolitan Authority)? They do give you methadone, after all.”<sup>7</sup>

Until laws and policies are in place to help avert a health crisis rather than perpetuate one, trials such as the Thai tenofovir study will raise serious questions. In the absence of complete HIV prevention tools based on needs defined by the community under study, such trials are ethically indefensible and should not take place.

The issues raised by the tenofovir study also underscore some of the larger problems of how pervasive negative attitudes toward drug users, fueled by political initiatives such as Thailand’s recent drug war, foster intolerance toward groups that need immediate humane and evidence-based protections for their health and human rights. Scientists and activists in rich countries that can afford access to patented pharmaceutical products may be able to take the longer view. But groups like injecting drug users in Thailand may see only more sickness and death in their future if researchers and community advocates do not work harder to find more common ground in their efforts to fight HIV/AIDS.

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HIV epidemics among IDUs in 2005 are largely preventable. If we could use the full tool kit of prevention services where these epidemics are occurring, we could dramatically reduce transmission and bring infection rates down to the very low levels seen where prevention has been taken to scale.

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## HIV Prevention Research among IDUs in Prevention-Limited Settings: Ethics, Human Rights, and Research Priorities

Chris Beyrer\*

The emerging and ongoing global epidemics of HIV-1 among injecting drug users (IDUs) in 2005 are stark evidence of the need to implement existing prevention tools *and* to develop and test new ones. In settings that have full access to HIV prevention services for IDUs and high coverage rates of those services, HIV spread among IDUs has been well controlled. Yet such settings are uncommon, and are particularly rare in developing countries. In a 2004 global review, one group estimated that roughly four out of five IDUs worldwide lived in developing, not developed, countries [Aciejas et al. 2004].

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Vaccines have long been shown to be among the most effective prevention strategies for prevention of viral infectious diseases, but have particular importance in low-resource settings because of their marked cost-effectiveness. In addition to continuing efforts to find a vaccine, the global roll-out of antiretroviral (ARV) therapy now underway will demand increased use of effective strategies including harm reduction, drug treatment on demand, and peer outreach and education to maximize adherence, access, and the clinical benefits of ARV therapy. Efforts to develop and test a safe and effective HIV vaccine will require IDU-specific research, as many immunologists and vaccinologists think that developing a vaccine against low efficiency sexual exposure is more possible than a vaccine against the kinds of direct bloodstream exposures thought to lead to HIV infection in IDUs and blood products recipients [Beyrer 2002].

We don't have the science to answer this question directly. But it is likely that we will only really understand HIV vaccine efficacy in sexual versus parenteral exposure when we have better vaccines, and when we can conduct definitive trials. Currently, it is clear that we will only develop those future HIV vaccines through clinical trials in human volunteers.

Prevention research generally is essential to investigate pre-exposure prophylaxis approaches, new substance use treatments and programs, and novel social, behavioral, and structural interventions to prevent HIV [Page-Shafer et al. 2005]. These would seem to be uncontroversial assertions. Yet HIV prevention research for IDU populations has been an arena of increasing controversy and debate [Chua et al. 2005]. But what have been the drivers of contention in the field? And how might communities, researchers, and decision makers respond to these concerns more effectively and ensure that new and beneficial technologies and approaches reach individuals and communities at risk?

## Prevention Trials and the Need for Incidence Measures

While there are many approaches to measuring the impact of interventions, the gold standard for tests of efficacy is randomized and controlled trials. Prevention trials are a subset of such trials, and have generally used similar methods to other kinds of trials. Where prevention trials differ most fundamentally from others is that prevention trials generally require not already infected or ill participants, but healthy uninfected volunteers who are at risk for the outcome of interest. For HIV prevention research with an outcome of new, or incident, HIV infection, this means enrollment of HIV-negative but at-risk individuals. This is in marked contrast to the clinical trials through which research developed highly active antiretroviral therapy (HAART), and which required trial participants with HIV infection and/or clinical AIDS. In the AIDS drug trial effort,

patients demanded access to clinical trials and communities and researchers jointly saw them as a key way of improving access to new therapies, supporting AIDS clinic infrastructures, and working together to reach effective therapy. Indeed, the AIDS Clinical Trial Group, ACTG, which did so many of the key trials leading to triple therapy has been seen as a model of cooperation between researchers, affected communities, and the government sponsor (the Division of AIDS of the National Institute of Allergy and Infectious Diseases of the NIH). Prevention trials are very different. They generally require that either very high risk individuals be recruited, or enrollment numbers must be very large to measure prevention impacts. Most of the participants will not become HIV infected, and will likely derive little, if any, personal benefit from participation. Nevertheless, to measure prevention efficacy, or its absence, substantial numbers must be recruited, and incidence rates need to be high enough to make comparisons possible. This is true for HIV prevention trials in all transmission settings: prevention of mother-to-child transmission; and of trials aimed at prevention of sexual transmission, such as vaginal microbicide trials and the several male circumcision studies either underway or recently completed, as well as in trials for prevention of HIV infection among IDU. The scale of these undertakings, and their cost, can be enormous. The first HIV vaccine trial to test efficacy (the VAXGEN trials of AIDSVAX) enrolled over 5,400 HIV-uninfected but at risk gay and bisexual men and cost over 200 million dollars [Colfax et al. 2005]. Several vaginal microbicide trials in 2005 included thousands of participants. A large vaginal microbicide trial conducted in Ghana, West Africa, which used HIV infection as its endpoint, was prematurely halted due to HIV infection rates that were too low [Family Health International 2005]. Studies with low infection rates, like this one, are generally deemed unfeasible. From an ethics perspective, it becomes ethically difficult to justify risks, however minimal, to participants, if it is clear that the studies will be unable to address the primary questions they were designed to answer.

Because of their scale, complexity, and cost, HIV prevention trials have led investigators to seek populations and settings where HIV incidence rates—at individual and population levels—can support successful trials. As an example, prevention of mother-to-child transmission trials can no longer feasibly be done in the United States and Western Europe because the rates of transmission are simply too low and the numbers of pregnant women with HIV infection in any one clinic or hospital in a year are too low to make research feasible. While this is wonderful from a humanitarian and public health perspective, it does not make research feasible. In 2004, the entire United States had fewer than 200 HIV-infected births in a population of over 280 million citizens [CDC 2005]. In contrast, there are many countries in southern Africa where more than one out of every five pregnant women are HIV-infected, and where new drugs and therapies to prevent mother-to-child transmission can be evaluated in one hospital in a matter of months. A study of vaginal washing to prevent transmission during labor

successfully enrolled over 3,300 mothers with HIV infection in one hospital in Malawi over a three month period [Taha et al. 1997]. It is simply sound science to implement prevention research where disease incidence is high, and questions can be most efficiently answered. Vaginal microbicides must be tested in large scale trials where HIV incidence rates among those at sexual risk are high enough to make such trials feasible. And by extension, HIV prevention studies among IDUs need to be done where HIV infection rates are high enough to measure the impact of new interventions. The Bangkok trial of the VAXGEN product AIDS-VAX B/E is a good example of this kind of research. This study enrolled over 2,500 IDUs in Bangkok, and reached a definitive trial outcome (no efficacy of the candidate vaccine) in timely fashion, and with a trial about half the size of the related trial among gay and bisexual men in the United States, Canada, and the Netherlands [Pittisuthitum 2005].

Does this not imply that HIV prevention trials, including vaccine trials and microbicide trials, actually require some study participants to become HIV infected in order to answer questions of efficacy? Yes. Prevention trials in which too few participants become infected are underpowered, to use a statistical term, and do not allow researchers to assess if a given intervention worked to prevent infection. This is especially relevant for those interventions, like HIV vaccines, where there is no product with any evidence of efficacy. In such cases, experimental arms of trials can only be compared to placebos—we have nothing else with which they can be reasonably compared since nothing has been shown to work. This is acceptable ethically as long as researchers make it clear to all volunteers that they may be randomized to a “real” drug or vaccine or to a placebo arm. And it is acceptable as long as every participant receives a minimum standard of HIV prevention services. These services generally include individualized HIV risk reduction counseling, preventive education, and a minimum standard of HIV prevention tools. In sexual transmission trials such as vaginal microbicide trials, this minimum package has included counseling, education, free condoms at study visits, and treatment for selected sexually transmitted diseases [Van Damme et al. 2002]. These measures can often reduce the HIV incidence rate in a study cohort by as much half. Trials are usually designed with large numbers of participants and conservative estimates of infection rates to address the declines that good basic prevention efforts can achieve.

The issue of what basic prevention constitutes for parenteral transmission trials among IDUs would seem straightforward. Yet this issue has become a key area of contention on ethical and human rights fronts for IDU related research.

## Prevention Standards for Trials

To deal with the reality that prevention trials must offer prevention services and that these services will generally reduce HIV risks and rates, making it harder to measure new prevention approaches, the research and ethics communities have come to a consensus: prevention services have to be offered to all participants in trials where HIV infection is an outcome, and these trials must be designed such that they will still have enough infections *after* the best prevention efforts have been offered to all participants to be able to yield measurable results. This can be called *the residual incidence*: the rate of new HIV infections which remain in a trial population after we have given prevention our best effort. This has increased the size and cost of prevention trials, but has also helped ensure participant, community, and political support for these critical studies. Since trials in most fields and for virtually all licensed vaccines now in use have been iterative in nature—requiring multiple large field trials over years or decades to achieve success—the long-term support for HIV prevention trials in the communities where they are mounted is of critical import. Page-Shafer and colleagues, writing about planning an efficacy trial to study the use of pre-exposure prophylaxis with the antiviral drug tenofovir (tenofovir disoproxil fumarate) to prevent HIV infection among female sex workers in Cambodia, described the package of prevention services they argue meet the minimum standard:

The best standard of care for HIV prevention in individuals that is currently available is the provision of information about HIV transmission and how infection can be avoided, condoms to people who may be at risk through sexual exposure, and sterile injecting equipment to people at risk through injection practices [Page-Shafer et al. 2005].

The Cambodian tenofovir trial was halted in 2004 by the Cambodian government due to concerns raised by community groups, including concerns about the prevention standard and whether the researchers were deliberately planning to limit prevention in order to have high HIV-infection rates. This allegation was vigorously denied by the investigators, who maintained that they would provide quality counseling, preventive education, and condoms, for a study population at sexual risk [Page-Shafer et al. 2004]. Whatever lessons can be derived from this unfortunate situation, one clear outcome is that researchers and communities need to address concerns about prevention packages in prevention trials early, openly, and together, if outcomes like the Cambodian tenofovir trial are to be avoided in the future. We need prevention research and an HIV vaccine, and we will only get these as a global community if prevention standard issues are addressed.

What then is the minimum package of prevention services that ought to be provided to IDU participants in prevention trials? The evidence from two decades of research in this arena is clear: IDUs should be provided with individualized risk reduction counseling, which should include assessment of both their injection and sexual risks for HIV acquisition; IDUs should be provided condoms for prevention of sexual transmission; IDUs should be provided clean needles and syringes to reduce their risk of needle sharing. Some would argue that there is an additional component to this basic package: IDUs should be provided at least referral, and with a reasonable expectation of access, to drug treatment if they want it, and with treatment regimes with evidence of efficacy for HIV prevention, such as methadone maintenance therapy (MMT). And this is where the issue becomes complicated. While the science of prevention of HIV infection through injecting drug use transmission is relatively straightforward, the policy environment around these prevention technologies has been fraught with complexity. The United States maintains a federal ban on funding for needle and syringe exchange programs (NSEPs) and has enforced this ban in international programs receiving U.S. federal dollars for support. Many countries have followed the U.S. lead, making NSEPs a grossly underutilized prevention tool worldwide. But the United States does not oppose drug treatment and substitution therapy, and is currently funding new HIV prevention research evaluating suboxone as an HIV prevention tool for IDUs through the HIV Prevention Trials Network (HPTN) of the National Institutes of Health. Russia, many FSU states, and, until recently, China, in contrast, have allowed NSEP, but continue to ban methadone and other opiate substitution approaches [Beyrer 2003]. The United States has proven as ideological and inflexible about NSEPs as the Russians have been about methadone. In this context, provision of minimum standards of prevention services swiftly becomes as much a question of political and human rights as it is one of public health or bioethics.

Why not then simply mount HIV prevention trials among IDUs where the minimum prevention standard is available? Where all the basics including NSEPs, a favorable policy environment, and drug treatment on demand for IDUs who want it are available, but where there are still large enough populations of active IDUs in which to mount trials? These standards could be met without conflict in Australia, or the UK, or in Brazil, or even in states within the United States where NSEPs are provided by local funds and not federal dollars. The fact of the matter is that settings where all these prevention minimums are in place *do not have high HIV infection rates among IDU*. Where HIV is spreading explosively among IDUs are those communities, cities, countries, and indeed whole regions where prevention services are currently not available, not taken to scale, or outright banned [Beyrer 2003]. This highlights a simple truth: HIV epidemics among IDUs in 2005 are largely preventable. If we could use the full tool kit of prevention services where these epidemics are occurring, we could dramatically reduce transmission and bring infection rates down to the very low levels seen where prevention

has been taken to scale. The Australian effort, where the national government in 2002 completed a 10-year review of their prevention programs, is perhaps the best described example. Australia estimated that it prevented 25,000 cases of HIV infection, 21,000 cases of HCV, and on an investment of about 150 million Australian dollars, saved somewhere between 2.4 and 7.7 billion dollars by taking harm reduction to scale [Australian National Council on Drugs 2002]. Applied elsewhere, this approach could enormously reduce the scale and scope of the current epidemics without an HIV vaccine or any other new technology. Yet in 2004 the world's fastest growing epidemics, those in the former Soviet Union, Central Asia, and Eastern Europe, were all characterized by IDU predominance and limits on effective prevention technologies.

Pragmatism forces us to recognize that even though scientific evidence shows that a public health tool works, it may not be sufficient to change policy. Advocates for prevention efforts and treatment of IDUs in the United States have been told by well meaning congressional staff that for some leaders maintaining the needle and syringe exchange ban has become a point of honor, akin to being “tough on drugs” and “tough on crime.” The ban has become a shibboleth, a sacred cow that it would be better to not waste time and effort on attempting to reverse. Methadone has also become such a politically weighted drug that in some settings, especially in Russia and the FSU, it may be more productive to develop and test politically acceptable alternatives such as vaccines than to expend years or decades pushing for methadone licensure and/or expanded use.

Pragmatism would argue that—*given the restrictions* on prevention and the political realities for drug using communities (and politicians)—interventions with the potential to impact HIV epidemics worldwide ought to be tested. From this perspective, an HIV vaccine is arguably less politically weighted than providing drug treatment or reversing the NSEP ban. Indeed, one of the potential advantages for suboxone is its limited ability to provide a “high” of any type, hence its appeal to those who oppose methadone and buprenorphine alone on the basis that they have some abuse potential. A pragmatic approach could be to conduct research on new prevention strategies which might overcome the political barriers faced by earlier interventions. If we accept this pragmatic approach, we still must address the question of where such trials might be conducted, and what prevention packages for participants will include.

## Prevention Research and the Human Rights Context

The Universal Declaration of Human Rights of 1948 applies just as much to drug users as to any other group or individual. Human beings do not lose their fundamental human rights because they use drugs or drink alcohol, or become addicted to any one of the

multitude of addictive substances people use. Nevertheless, human rights violations against drug users including discrimination, state violence, torture, arbitrary detention, and extrajudicial execution are common and can be found worldwide. They can also have profoundly negative impacts on HIV prevention [Wodak 2004].

While HIV prevention trials clearly need to occur where HIV infections are high enough to answer key questions, those proposing trials must balance the risk for human rights violations against the need to be in rapidly expanding epidemic zones. At the extreme end of the rights spectrum this becomes relatively easy: no one would argue that an HIV vaccine trial among drug users in autocratic Belarus or in collaboration with the Burmese junta would be able to provide assurances for the protection of the human rights of participants. Where this becomes more challenging is in settings where there is the rule of law, and where states are signatory to human rights instruments and conventions, but where the specific rights situation for drug users is problematic. For example, Thailand has achieved remarkable success in preventing school and workplace discrimination based on HIV status, has implemented widespread public access to ARV therapy, and is generally credited with a humane and effective response to the spread of HIV [Ainsworth et al. 2003]. Yet Thailand's 2003 "War on Drugs" policy, led by Prime Minister Thaksin Shinawatra, resulted in over 2,200 extrajudicial executions, and was quite literally a reign of terror for drug users and their families [Human Rights Watch, 2004].

It is also the case that while researchers and their partners (communities, participants, and clinic and hospital staff) generally negotiate with ministries of health to conduct trials, it is rarely within health ministries that rights violation issues arise. It is almost invariably police and security forces who harass drug users and who have the potential to disrupt or undermine the regular and intensive study visits that participants in prevention trials are usually asked to attend. And as with police harassment of needle and syringe exchange sites, it is these kinds of abuses which can cause the greatest concern for trial participants. Unfortunately, in many settings, health officials and staff have much less ability to affect security and criminal justice policy than interior and justice ministries.

## Research and Advocacy Synergies: "Skillful Means"

Clearly, researchers and advocates need more effective HIV and HCV prevention tools for drug users. And the world needs an HIV vaccine that works against both sexual and parenteral exposure to HIV infection. These goals will only be reached through scientifically and ethically sound research. Yet the potential conflicts between researchers and

drug users could threaten this enterprise. IDUs and their advocates are absolutely right to argue for the highest standards of prevention available for trial participants. But this advocacy effort too, or at least the way it has been conducted, can undermine the goal of developing and testing more and better prevention tools.

While advocates have rarely had the power to stop governments from implementing wrong-headed policies (i.e., the inability to overturn the needle and syringe exchange ban under both the Clinton and Bush administrations, and the Russian rigidities over opiate substitution), advocates can stop trials. This is because science is utterly dependent on voluntary participation, and because communities have real power through community advisory boards and other mechanisms to weigh in on the research enterprise. While researchers can seem powerful compared to drug users, the prevention trials undertaking as a whole is remarkably fragile: funds are soft, ethical and human subject reviews intense, and support within the scientific community for research on IDUs is spotty at best. Researchers in this arena have to make extraordinary efforts to convince their colleagues and their funders that IDU trials are important science and are logistically feasible, and they are highly vulnerable to the charge that their work is not supported by the very communities they seek to serve. With limited funds for prevention research, and much more politically appetizing targets like prevention of mother-to-child transmission research and vaginal microbicides for women-controlled prevention methods, the IDU research effort is easily marginalized.

So what is the way forward? There are already countless relationships and alliances between researchers and advocates—and there are many people with feet (or hearts) in both worlds. People of good intent abound on all sides of this debate. A potentially useful approach called “skillful means” comes from Buddhist teachings. “Skillful means” refers to the use of all of shared intelligence, skills, and compassion to advance a common goal (the end of AIDS) in ways that avoid disruptive open confrontations and heated political conflicts that can stop progress. “Skillful means” is strategic thinking, and alliance building, and requires an astute understanding of an adversary’s interests. For example, say a rich country is supporting an HIV prevention trial for IDUs in a poor country. The donor opposes needle and syringe exchange and refuses to pay for it, or to condone even counseling about safe injection practices for trial participants. The community of IDUs and their allies in the trial site setting insist that needles and syringes are part of the international standard and must be provided. A skillful means approach would bring the researchers together with the community, however informally, to work out ways in which the donor could be assuaged that none of the donor dollars were going to support needle and syringe exchange, and yet every participant in any part of the trial would get both counseling and safe injection equipment at every visit. How? The researchers and the IDU community could work together and seek separate funding for an NSEP that would operate in the same settings where the trial was being

conducted. Trial participants might have a community representative or advocate on hand to provide information about where to access the services. Community members could be part of staff training for these efforts, to ensure that issues of discrimination and stigma would not limit participation or access to prevention. All of this could be done in a parallel access approach that would meet the trial sponsor's political agenda (not openly supporting or funding harm reduction) as well as the goals of researchers and the IDU community to conduct research that meets the highest ethical and human rights standards. This kind of close and active collaboration is likely to be critical if the IDU research effort is to succeed. It already happens in many contexts, and there are many models of success. We need to do more of it—and with more strategic thinking and compassion.

The IDU research effort faces ethical hurdles in providing evidence based prevention services when these are politically fraught. And researchers face human rights challenges when trials occur in settings where rights violations of IDUs are common. While these issues pose significant challenges, a potential way forward may be through strategic alliances with those who have genuine concern for ending AIDS, and for reducing the harms of drug use. Progress can be made if researchers and advocates get smarter and work together more closely to effectively manage their complex relationships with donors and governments. The strengthening of cooperation between researchers and IDUs represents a new opportunity for creating potent synergies to challenge the discrimination, inequity, and pain perpetuated by HIV/AIDS.

# Notes

## Foreword

1. WHO. "Cause of antiretroviral treatment status in South-East Asia as of June 2005." Chart presented by WHO, available online at: [http://w3.whosea.org/EN/Section10/Section18/Section2009\\_9934.htm](http://w3.whosea.org/EN/Section10/Section18/Section2009_9934.htm).
2. Personal communication with Karyn Kaplan, Thai AIDS Treatment Action Group, May 26, 2006.

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11. See Phillipp du Cros and Adeeba Kamarulzaman in this volume, "HIV and Tuberculosis Coinfection."
12. For a review of recent research on this subject, see for example: Grabowski J, Shearer J, Merrill J, Negus, and S Stevens. Agonist-like, replacement pharmacotherapy for stimulant abuse and dependence. *Addictive Behaviors*. 2004; 29: 1439–1464.

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## Adherence to Antiretroviral Treatment in HIV-Infected Drug Users: The Role of Psychosocial Factors and Opiate Substitution Therapy

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## The GLOBUS Project: First Steps to Antiretroviral Therapy for Injection Drug Users in Russia

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## The Natural History of HIV and Hepatitis C Coinfection

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## Clinical Trials and Active Drug Users: A Story of Unmet Needs

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# Tables

## Recreational Drugs and Opiate Substitution Medications: Interactions with Antiretrovirals

**Table 1. Metabolic characteristics of antiretrovirals<sup>8-13</sup>**

<b>Drug class</b>	<b>Enzyme inhibitors</b>	<b>Enzyme inducers</b>
Non-nucleoside reverse transcriptase inhibitors	Delavirdine – inhibits CYP3A4 Efavirenz – inhibits CYP2B6, 3A4, 2C9/19	Nevirapine and efavirenz induce CYP3A4
Protease inhibitors	Ritonavir: (in descending order of potency of inhibition) 3A4>2D6>2C9>2C19>>2A6>2E1  All other PIs inhibit CYP3A4 Amprenavir also inhibits CYP2C19 Nelfinavir, ritonavir also inhibit CYP2B6	Ritonavir, nelfinavir and tipranavir induce glucuronyltransferase. Atazanavir inhibits glucuronyltransferase.  Tipranavir induces CYP3A. Ritonavir induces 1A2 and may induce 3A4. Occasionally, amprenavir may induce 3A.

Key: CYP = cytochrome P450

**Table 2: Interactions between antiretrovirals and “rave” drugs<sup>20, 23-25, 27-31, 36-43, 46, 47</sup>**

<b>Drug</b>	<b>Metabolism</b>	<b>Actual/theoretical interaction</b>	<b>Potential significance</b>	<b>Recommendation</b>
Amphetamines	CYP 2D6 <sup>29-31</sup>	Possible ↑ levels with ritonavir.	Hypertension, hyperthermia, seizures, arrhythmias, tachycardia, tachypnea. 1 death possibly related to methamphetamine interaction with ritonavir/saquinavir reported (see text)	Avoid combination with ritonavir if possible; alternatively, start with ¼ - ½ of initial amount of amphetamine used.
Gamma hydroxy-butyrate (GHB)	Expired breath as CO <sub>2</sub> First pass metabolism <sup>36, 37</sup>	Possible ↑ levels/prolonged effect with antiretrovirals, especially ritonavir.	1 case GHB toxicity with ritonavir/saquinavir. <sup>38</sup> Myoclonic or seizure activity, bradycardia, respiratory depression, loss of consciousness.	Use cautiously with inhibitors of the cytochrome P450 system (i.e., PI’s, delavirdine, efavirenz). Ensure patient aware of signs/symptoms of GHB toxicity.
Ketamine	CYP 2B6 (main) 3A, 2C9 (both to lesser extent) <sup>39-42</sup>	Possible ↑ levels with antiretrovirals, especially with ritonavir, nelfinavir and	Respiratory depression, loss of consciousness, hallucinations.	Use cautiously with inhibitors of the cytochrome P450 system,

Drug	Metabolism	Actual/theoretical interaction	Potential significance	Recommendation
		efavirenz.		especially ritonavir, nelfinavir and efavirenz. Ensure patient is aware of signs/symptoms of ketamine toxicity.
Lysergic acid diethylamide (LSD)	Unknown <sup>46, 47</sup>	Caution with antiretrovirals	Hallucinations, agitation, psychosis, “flashbacks”	Use cautiously with inhibitors of the cytochrome P450 system (i.e. PI’s, delavirdine, efavirenz). Ensure patient aware of signs/symptoms of LSD toxicity.
Methylenedioxy-methamphetamine (MDMA), “Ecstasy”	CYP 2D6 (30%); CYP2B6, 3A4 and 1A2 also involved <sup>23-25</sup>	Possible ↑ levels with PIs, delavirdine.	1 death reported (see text) <sup>20</sup> Hyponatremia, hyperthermia, arrhythmias, tremor, hyperreflexia, sweating, seizures, tachycardia, rhabdomyolysis.	Avoid combining with ritonavir if possible. Alternatively, advise patient to use ~ ¼ - ½ of usual amount used, and watch for signs of MDMA toxicity. Other precautions include staying well hydrated at

<b>Drug</b>	<b>Metabolism</b>	<b>Actual/theoretical interaction</b>	<b>Potential significance</b>	<b>Recommendation</b>
				party, avoiding alcohol and taking breaks from dancing.
Phencyclidine (PCP)	CYP 3A <sup>43</sup> , CYP2C11 <sup>44</sup> , inhibits CYP2B1 <sup>45</sup>	Possible ↑ levels with antiretrovirals	Seizures, hypertension, rhabdomyolysis, hyperthermia	Use cautiously with inhibitors of the cytochrome P450 system (i.e. PI's, delavirdine, efavirenz). Ensure patient aware of signs/symptoms of PCP toxicity.

Key: CO<sub>2</sub> = carbon dioxide, CYP = cytochrome P450

**Table 3. Interactions between antiretrovirals and methadone.**<sup>52-78</sup>

Antiretroviral	Study type	Patient(s)	Nature of interaction	Recommendation
<b>NNRTI's</b>				
Delavirdine <sup>70</sup>	Pharmacokinetic	16 HIV-negative volunteers maintained on methadone and 15 controls, each treated with delavirdine 600 mg bid for 5 days.	Methadone did not alter pharmacokinetics of delavirdine or N-delavirdine. Effect of delavirdine on methadone not studied.	Since delavirdine an inhibitor of 3A4, monitor for symptoms of opiate toxicity (e.g., miosis, drowsiness, ↓ rate and depth of respiration, N/V, constipation, bradycardia, hypotension) until further data available.

<b>Antiretroviral</b>	<b>Study type</b>	<b>Patient(s)</b>	<b>Nature of interaction</b>	<b>Recommendation</b>
Efavirenz <sup>52</sup>	Pharmacokinetic	11 patients on stable methadone maintenance, due to begin antiretroviral therapy with two reverse transcriptase inhibitors and efavirenz	EFV ↓ methadone Cmax (p=0.007) and ↓ methadone AUC by mean of 60%. 9/11 patients complained of symptoms of methadone withdrawal from day 8-10 onwards of starting efavirenz, and received ↑ in methadone dose in increments of 10 mg until symptoms resolved (mean ↑ in methadone dose required: 22%)	Monitor for symptoms of opiate withdrawal (e.g., lacrimation, rhinorrhea, diaphoresis, restlessness, insomnia, dilated pupils, piloerection) and adjust methadone dose if necessary.
Efavirenz <sup>54</sup>	Case report	1 patient on methadone 100 mg a day for over one year; switched from nelfinavir/lamivudine/stavudine to an efavirenz containing regimen.	Four weeks after the introduction of efavirenz, patient reported tiredness, headache, cold sweats and shivering. Concentrations of (R)-methadone (active enantiomer of methadone) before and after the introduction of efavirenz were 168 and 90 ng/ml, respectively. Dose of methadone ↑ to 180 mg/day before symptoms disappeared.	

Antiretroviral	Study type	Patient(s)	Nature of interaction	Recommendation
Efavirenz <sup>71</sup>	Case report	3 HIV infected IV drug users on methadone treatment.	Opiate withdrawal symptoms emerged 4 to 7 days following the introduction of efavirenz. Methadone levels were obtained in one patient and were 65% lower with efavirenz than at baseline. Patients required a 66-133% ↑ in methadone dose to compensate.	
Nevirapine, then Efavirenz <sup>55</sup>	Case report	Patient stabilized on methadone 40 mg daily. Antiretroviral therapy changed from zidovudine/lamivudine to d4T/ddI/nevirapine, and later d4T/ddI/efavirenz.	2 days following change, patient experienced symptoms compatible with opiate withdrawal (i.e. cramps, tremor, rhinorrhea etc). Symptoms stopped with the discontinuation of nevirapine, and recurred with nevirapine rechallenge. Symptoms recurred again following change to efavirenz, in spite of dose ↑ to 80 mg/day. Methadone levels stable despite dose increase.	

<b>Antiretroviral</b>	<b>Study type</b>	<b>Patient(s)</b>	<b>Nature of interaction</b>	<b>Recommendation</b>
Nevirapine <sup>53</sup>	Case report	1 patient on methadone 80 mg/day for 3 years; switched from ddI/d4T/SQV-hgc/NFV after 1 month (because of ddI intolerance) to d4T/NFV/SQV-sgc/nevirapine.	One week following the change to a nevirapine containing regimen, the patient experience symptoms of methadone withdrawal (total body pain, nausea, vomiting, insomnia, sweats, sense of impending doom). Over the course of 4 weeks, the dose ↑ to 130 mg/day and her symptoms resolved.	Monitor for symptoms of opiate withdrawal (see under “Efavirenz”) and adjust methadone dose if necessary.
Nevirapine <sup>57</sup>	Retrospective chart review.	7 patients on chronic methadone maintenance following initiation of treatment with nevirapine containing regimens.	Methadone withdrawal precipitated in all patients within 4-8 days of initiating treatment with nevirapine. Methadone levels were determined for 3 patients, and were subtherapeutic in each case. Dose ↑ necessary and 4 patients chose to discontinue therapy.	

Antiretroviral	Study type	Patient(s)	Nature of interaction	Recommendation
Nevirapine <sup>58</sup>	Case series	5 patients on methadone maintenance program starting nevirapine based HAART.	4 of the 5 patients exhibited symptoms consistent with opiate withdrawal 6-15 days after beginning nevirapine therapy. Two patients discontinued therapy; two patients remained on therapy but required ↑ in methadone dose of 33% and 100%.	
Nevirapine <sup>56</sup>	Prospective study	45 intravenous drug users, stabilized on methadone and treated with nevirapine, didanosine and lamivudine, all once a day.	30% of the 45 patients required ↑ in their methadone dose due to withdrawal symptoms.	

<b>Antiretroviral</b>	<b>Study type</b>	<b>Patient(s)</b>	<b>Nature of interaction</b>	<b>Recommendation</b>
Nevirapine <sup>75</sup>	Pharmacokinetic study	8 patients on stable daily methadone, beginning treatment with nevirapine based HAART.	Nevirapine ↓ methadone AUC by a mean of 50%. 6 of the 8 patients reported symptoms of methadone withdrawal from days 8-10 onwards of starting nevirapine, and received an ↑ in methadone dose in increments of 10 mg (mean ↑ in methadone dose required: 16%).	
Nevirapine <sup>167</sup>	Pharmacokinetic study	24 patients on stable methadone, beginning treatment with nevirapine based HAART. 12-hour PK measurements done at baseline and after 28 days.	Nevirapine ↓ methadone AUC by mean of 40%; mean methadone dose ↑ by 24% (range 0-80%) during study.	
<b>PI's</b>				
Amprenavir (+ abacavir) <sup>168</sup>	Pharmacokinetic study	Methadone blood concentrations were measured in five addict patients receiving	Methadone concentrations ↓ by 35% (range 28-87%, p = 0.043). Two patients reported on several occasions nausea in the morning before the intake	

Antiretroviral	Study type	Patient(s)	Nature of interaction	Recommendation
		methadone maintenance therapy before and after introduction of abacavir plus amprenavir for 14 days.	of the daily methadone dose, which is suggestive of a withdrawal reaction.	
Amprenavir <sup>169, 170</sup>	Pharmacokinetic study	16 opiate dependent, HIV-patients on at least 30 days stable methadone treatment; methadone levels reassessed after 10 days of amprenavir 1200 mg bid.	Prospective, open-label study in HIV-negative subjects (n=19) maintained on methadone for at least 30 days, addition of amprenavir 1200 mg BID for 10 days resulted in delayed APV absorption, 13% ↓ AUC, 21% ↓ C <sub>min</sub> of active methadone enantiomer. The inactive S-enantiomer AUC and C <sub>min</sub> were decreased by 40% and 52%, respectively. No clinical evidence of methadone withdrawal was observed, and no methadone dosage was adjusted in any patient.  Compared to a non-matched historical control group, a 30%, 27%, and 25% ↓	Methadone dosage adjustment likely not necessary when coadministered with amprenavir. Monitor for amprenavir efficacy.

Antiretroviral	Study type	Patient(s)	Nature of interaction	Recommendation
			in AUC, Cmax, and Cmin of amprenavir was observed. Clinical significance unclear.	
Indinavir <sup>76</sup>	Pharmacokinetic	12 HIV + patients on methadone 20 – 60 mg per day; indinavir 800 mg po q8h added.	No significant effect of indinavir on methadone AUC when compared to historical controls. No significant effect of methadone on indinavir AUC, but ↑ indinavir Cmin 50-100% and ↓ indinavir Cmax 16-36%, all vs. historical controls.	Combination appears safe.
Indinavir, Nelfinavir, Ritonavir, Saquinavir <sup>65</sup>	Case series	Methadone levels measured prior to and at least one week following addition of a PI to stable dual RTI therapy in ten patients on methadone maintenance program.	Methadone concentrations unchanged in six patients switched to indinavir and one patient switched to saquinavir; methadone steady state concentrations ↓ 40-50% in one patient switched to ritonavir and two patients switched to nelfinavir.	Monitor for symptoms of opiate withdrawal (see under “Efavirenz”) with nelfinavir and ritonavir; adjust methadone dose if necessary.

<b>Antiretroviral</b>	<b>Study type</b>	<b>Patient(s)</b>	<b>Nature of interaction</b>	<b>Recommendation</b>
Lopinavir/ ritonavir (Kaletra) <sup>171</sup>	Pharmacokinetic	11 healthy volunteers received a single 5 mg dose of methadone. Methadone levels measured prior to and following 10 days of lopinavir/ritonavir (400mg/100mg twice a day).	Lopinavir/ritonavir ↓ methadone AUC and Cmax 47%.	Observed decreases in methadone levels not always associated with opioid withdrawal symptoms; possible that lopinavir/ritonavir may produce stereoselective induction of methadone metabolism that would differentially decrease concentrations of the inactive S-isomer more than the active R-isomer.
Lopinavir/ ritonavir vs. ritonavir <sup>172</sup>	Pharmacokinetic	In two parallel, PK studies, healthy subjects on stable methadone received 7 days of either lopinavir/ritonavir 400/100 mg BID or ritonavir 100 mg BID.	Methadone AUC ↓ 26%, Cmax and Cmin ↓ 28% in presence of lopinavir/r, and was associated with a significant ↑ in number of opiate withdrawal symptoms. In contrast, methadone PK were not affected by ritonavir alone.	Likely no need for

<b>Antiretroviral</b>	<b>Study type</b>	<b>Patient(s)</b>	<b>Nature of interaction</b>	<b>Recommendation</b>
Lopinavir/ritonavir <sup>173</sup>	Pharmacokinetic study	8 HIV-infected patients on methadone maintenance (median dose, 80 mg; range, 40–100 mg) initiated lopinavir/ritonavir plus 2 NRTIs.	A 36% ↓ in methadone AUC <sub>0–24h</sub> occurred after 14 days of lopinavir/ritonavir. However, none of the patients experienced opioid withdrawal symptoms or needed supplemental methadone added to their maintenance dose.	routine methadone dose adjustment when initiating lopinavir/ritonavir; however, as a precaution it is still recommended to

<b>Antiretroviral</b>	<b>Study type</b>	<b>Patient(s)</b>	<b>Nature of interaction</b>	<b>Recommendation</b>
Lopinavir/ritonavir <sup>174</sup>	Observational study	20 HIV-positive subjects maintained on methadone for >1 month initiated lopinavir/rtv HAART regimens. Changes in methadone dose and opioid withdrawal symptoms were assessed daily for 28 days. Median (range) methadone dose at study entry was 95 (40–130) mg/d. Two subjects did not complete the observational period.	None of the 18 assessable patients experienced symptoms of opioid withdrawal and no patients requested a change in methadone dosing during the evaluation period.	monitor for opioid withdrawal (see under “Efavirenz”) when initiating therapy.

<b>Antiretroviral</b>	<b>Study type</b>	<b>Patient(s)</b>	<b>Nature of interaction</b>	<b>Recommendation</b>
Nelfinavir <sup>60</sup>	Prospective pharmacokinetic study.	14 patients stabilized on a fixed methadone dose for at least 1 month before nelfinavir 1250 mg po bid for 8 days was added	Levels of (+)-methadone and (-)-methadone ↓ by 47% and 39%, respectively. No patient exhibited withdrawal symptoms, and no dosage adjustments were necessary.	Observed decreases in methadone levels not always associated with opioid withdrawal symptoms. Monitor for symptoms of opiate withdrawal (see under “Efavirenz”) and adjust methadone dose if necessary.
Nelfinavir <sup>63</sup>	Retrospective case series	75 patients on stable methadone dose started on nelfinavir.	2 of 75 patients needed slight ↑ in methadone dose (10 mg/day). Otherwise, no impact of nelfinavir on methadone.	
Nelfinavir <sup>64</sup>	Case report	Patient on stable methadone dose of 100 mg daily, indinavir and ddC; d4T and nelfinavir added to regimen.	Within 6 weeks of medication change, patient began to complain of opiate withdrawal symptoms, which ↑ in severity over 3 months. Methadone dose ↑ at 1-2 week intervals, and subtherapeutic methadone levels documented until dose of 285 mg/d attained.	

Antiretroviral	Study type	Patient(s)	Nature of interaction	Recommendation
Nelfinavir <sup>72</sup>	Pharmacokinetic	16 non-HIV infected volunteers on stable methadone dose for 4 weeks and 13 controls; received NFV 1250 mg po bid for 5 days.	Nonsignificant ↑ in median NFV 12 hour trough with methadone. 12 hour AUC of M8 53% lower vs. control.	
Nelfinavir <sup>73</sup>	Multi-site, retrospective	32 patients on stable methadone dose, receiving NFV based HAART; 84% of patients co-infected with hepatitis C.	17% of patients required methadone dose adjustments (mean 26 mg); otherwise, well tolerated combination.	

<b>Antiretroviral</b>	<b>Study type</b>	<b>Patient(s)</b>	<b>Nature of interaction</b>	<b>Recommendation</b>
Ritonavir/ Saquinavir <sup>59</sup>	Case report	1 patient on methadone 90 mg/day for 2 years. Antiretrovirals changed from indinavir/lamivudine/zidovudine to ritonavir/saquinavir/stavudine because of virologic progression.	One week following initiation of ritonavir containing regimen, patient was admitted to hospital with shakiness, diaphoresis, blurred vision, anxiety and hypotension. Methadone plasma level on admission was 210 ng/ml (within therapeutic range, however no levels prior to initiation of ritonavir). Methadone dose was gradually ↑ to 130 mg/day.	Monitor for symptoms of opiate withdrawal (see under “Efavirenz”) and adjust methadone dose if necessary.
Ritonavir/ Saquinavir <sup>175</sup>	Pharmacokinetic	12 HIV-negative volunteers on stable methadone dose evaluated before and after 14 days of once daily saquinavir/ritonavir (1600mg/100mg).	Clinically insignificant change in unbound methadone levels. 83% of subjects had C <sub>min</sub> of saquinavir > EC <sup>50</sup> .	

<b>Antiretroviral</b>	<b>Study type</b>	<b>Patient(s)</b>	<b>Nature of interaction</b>	<b>Recommendation</b>
Ritonavir/ Saquinavir <sup>61</sup>	24 hour pharmacokinetic study before and after 15 days of antiretroviral therapy to examine effect of ritonavir/saquinavir on methadone kinetics.	12 patients receiving stable methadone dose for at least 2 weeks.	↓ S-methadone AUC 40%, and ↓ R-methadone AUC 32%. However, when change in methadone AUC expressed in terms of unbound methadone, change in AUC was no longer significant; no evidence of opiate withdrawal.	

Antiretroviral	Study type	Patient(s)	Nature of interaction	Recommendation
Ritonavir/ Saquinavir <sup>78</sup>	Retrospective	18 HIV + patients beginning once daily therapy with ritonavir 100 mg and saquinavir – soft gel capsule 1600 mg and 5 HIV + patients beginning once daily therapy with ritonavir 200 mg and indinavir 1200 mg. All patients on methadone, 19 patients co-infected with hepatitis C.	No patient required methadone dose adjustment.	
Tipranavir <sup>176</sup>			50% ↓ methadone levels	Dosage of methadone may need to be increased when co-administered with tipranavir and 200 mg of ritonavir.
<b>Reverse Transcriptase Inhibitors</b>				

<b>Antiretroviral</b>	<b>Study type</b>	<b>Patient(s)</b>	<b>Nature of interaction</b>	<b>Recommendation</b>
Abacavir <sup>69</sup>	Pharmacokinetic study.	19 patients titrated to constant methadone dose ( $\geq 40$ mg/day) over 14 days. Days 15-28, received concomitant methadone and abacavir.	Slight $\uparrow$ in clearance of methadone by abacavir; no statistically significant change in C <sub>max</sub> , half-life or renal clearance of methadone. Methadone causes slight delay in rate but not extent of abacavir absorption.	Combination appears safe.
Didanosine buffered tablets (ddI), stavudine (d4T) <sup>66</sup>	Pharmacokinetic study	17 patients on methadone maintenance and 10 control patients. Two pharmacokinetic studies were completed for each study subject and control (one each for ddI and d4T).	d4T AUC $\downarrow$ 23% ddI tablets AUC $\downarrow$ 57% Effect primarily related to reduced bioavailability.	No data to guide dose adjustments. Monitor for virologic failure.

<b>Antiretroviral</b>	<b>Study type</b>	<b>Patient(s)</b>	<b>Nature of interaction</b>	<b>Recommendation</b>
Didanosine enteric-coated (EC) capsule <sup>81</sup>	Pharmacokinetic	HIV-negative patients (n = 17) on stable methadone dose; randomized to EC or tablet formulation, and crossed-over to alternative regimen after PK monitoring over 24 hours; comparisons made to historical data in non-methadone patients.	ddI buffered tablet: trend to decreased ddI AUC in presence of methadone.  EC formulation provided ddI plasma AUC levels comparable to historical controls in non-methadone patients.	Combination of EC capsule of ddI and methadone appears safe, no dosage adjustments necessary.

<b>Antiretroviral</b>	<b>Study type</b>	<b>Patient(s)</b>	<b>Nature of interaction</b>	<b>Recommendation</b>
Tenofovir <sup>177</sup>	Pharmacokinetic study	<p>13 HIV-negative subjects on stable methadone received 14 days of tenofovir 300 mg daily; kinetics of methadone and its R- and S-isomers done at baseline and on day 14.</p> <p>Short Opiate Withdrawal Scale (SOWS) questionnaire and pupillary diameter measurements also done at baseline and on day 14.</p>	<p>No change in kinetics of total methadone, R- and S-isomers when coadministered with tenofovir versus alone.</p> <p>No clinical or laboratory signs of opiate-related toxicity or withdrawal (including changes in SOWS scores or pupillary diameters) were noted.</p>	<p>Methadone pharmacokinetics and dynamics not affected by tenofovir.</p> <p>Combination appears safe.</p>

<b>Antiretroviral</b>	<b>Study type</b>	<b>Patient(s)</b>	<b>Nature of interaction</b>	<b>Recommendation</b>
Zidovudine <sup>67</sup>	Pharmacokinetic study	14 HIV-positive patients on methadone maintenance for at least 6 months and five control patients. Patients were receiving zidovudine 200 mg po every 4 hours.	Zidovudine AUC ↑ 43% vs. control. No effect on methadone maintenance.	Monitor for zidovudine related toxicities, such as nausea, vomiting, and bone marrow suppression. Other opioid pharmacotherapies
Zidovudine <sup>68</sup>	Pharmacokinetic within subject study.	8 patients started on acute methadone therapy as inpatients. Both oral and intravenous zidovudine pharmacokinetics determined before starting methadone, following acute methadone treatment and following two months of daily methadone.	Zidovudine AUC ↑ 41% during acute methadone treatment, and 29% during chronic treatment.	such as l-a-acetylmethadol LAAM, buprenorphine, or naltrexone not found to significantly affect zidovudine pharmacokinetics. <sup>178</sup>

Key: AUC = area under the concentration-time curve, bid = twice daily, C<sub>max</sub> = maximum plasma concentration, ddC = zalcitabine, ddI = didanosine, d4T = stavudine, EFV = efavirenz, HAART = highly active antiretroviral therapy, PI = protease inhibitor, NFV = nelfinavir, RTI = reverse transcriptase inhibitor, SQV-hgc = hard gel saquinavir

**Table 4 : Postulated and actual interactions between commonly used opiate drugs and antiretrovirals**<sup>96, 98, 108-113, 118, 179-182</sup>

Drug	Metabolism	Actual/theoretical interaction	Potential significance	Recommendation
Buprenorphine	<p>CYP3A4 and CYP2C8 isoenzymes responsible for approximately 65% and 30% of norbuprenorphine production, respectively.<sup>89</sup></p> <p>Buprenorphine and norbuprenorphine can act as inhibitors of CYP2D6 and CYP3A4, but these effects are not expected to be clinically significant at usual prescribed doses.</p>	<p><u>↓metabolism of buprenorphine:</u> via inhibition of CYP3A4</p> <p>In vitro studies confirm the potential for both ritonavir and indinavir to significantly inhibit buprenorphine metabolism<sup>90</sup>.</p> <p>Case report of three subjects on atazanavir 300/ritonavir 100 mg who experienced symptoms of opiate excess when initiated on buprenorphine 8-14 mg/day. In all cases, symptoms improved with reduction of buprenorphine to 8 mg daily or every other day. Potential mechanism may be due to CYP3A4 inhibition by atazanavir or ritonavir, or</p>	Potential opiate toxicity	<p>Close monitoring for signs and symptoms of opiate toxicity should therefore be exercised when combined use is undertaken.</p> <p>Until further data are available, initiate buprenorphine at reduced doses and titrate slowly.<sup>91</sup></p>

Drug	Metabolism	Actual/theoretical interaction	Potential significance	Recommendation
		inhibition of glucuronidation by atazanavir.		
		<p>↑ <u>metabolism of buprenorphine:</u> with CYP3A4 inducers such as nevirapine, efavirenz or tipranavir</p> <p>In a study of 15 HIV-negative opioid-dependent patients receiving chronic buprenorphine, the addition of efavirenz 600 mg per day for 15 days resulted in a 50% decrease in the AUC of buprenorphine.<sup>92</sup> No episodes of opiate withdrawal were observed.</p>	Potential for opiate withdrawal.	Monitor for withdrawal symptoms is warranted.
Codeine	3 pathways: Glucuronidation (UGT2B7, UGT2B4) to codeine-6-	<p>↓ <u>morphine levels:</u> 2D6 inhibition (inhibit O-demethylation)</p>	Opiate withdrawal, loss of analgesia	Monitor for signs/symptoms of opiate withdrawal (see

Drug	Metabolism	Actual/theoretical interaction	Potential significance	Recommendation
	glucuronide (~ 70-80 %) N-demethylation to norcodeine (3A4) ( $\leq 10\%$ ) O-demethylation to morphine (2D6) ( $\leq 10\%$ ) <sup>108-112, 179</sup>	3A4 or UGT2B7 induction (less substrate available for 2D6) <u><math>\uparrow</math> morphine levels:</u> 3A4 inhibition (shunting of substrate to 2D6 pathway)	Opiate toxicity	under “Meperidine”). Reassess level of analgesia.  Monitor for signs/symptoms of opiate toxicity (e.g., miosis, drowsiness, $\downarrow$ rate and depth of respiration, N/V, constipation, hypotension, bradycardia).
Meperidin (Demerol)	2 pathways: Hydrolysis to meperidinic acid by liver carboxylesterases and demethylation by cytochrome P450 system (2B6>3A4>2C19) to normeperidine <sup>181</sup>	AUC of meperidine $\downarrow$ 67% and AUC of normeperidine $\uparrow$ 47% in open label study of eight volunteers receiving treatment with 50 mg meperidine prior to and following 10 days of	Possible opiate withdrawal, loss of analgesia. Possible $\uparrow$ risk of seizures with normeperidine	Monitor for signs/symptoms of opiate withdrawal (e.g., lacrimation, rhinorrhea, diaphoresis, restlessness, insomnia, dilated pupils,

Drug	Metabolism	Actual/theoretical interaction	Potential significance	Recommendation
		treatment with ritonavir. <sup>96</sup>	accumulation.	piloerection). Reassess level of analgesia. Avoid combination of ritonavir and meperidine in patients with renal failure and patients who use meperidine regularly for analgesia or recreationally due to risk of neurotoxicity.
Morphine	Glucuronidated to morphine-6-glucuronide (M6G) by UGT2B7 and morphine-3-glucuronide (M3G) by UGT1A3 and UGT1A8 <sup>98, 118, 180</sup>	Induce UGT2B7: ↓ levels of morphine, ↑ levels of pharmacologically active M6G.	Possible opiate toxicity due to ↑ formation of M6G.	Monitor for signs/symptoms of opiate toxicity (see codeine).
Hydro-codone	CYP2D6 to hydromorphone CYP3A4 go norhydrocodone	↓ levels <u>hydromorphone</u> Inhibition of 2D6 3A4 induction (less substrate	Possible opiate withdrawal and loss of analgesia, although	Monitor for signs/symptoms of opiate withdrawal (see

Drug	Metabolism	Actual/theoretical interaction	Potential significance	Recommendation
		for 2D6 pathway)  <u>↑ hydromorphone levels</u> 3A4 inhibition (shunting to 2D6 pathway)	contribution of hydromorphone to analgesic effect not well established. Possible opiate toxicity.	under “Meperidine”). Reassess level of analgesia.  Monitor for signs/symptoms of opiate toxicity (see under “Codeine”).
Oxycodone	3 pathways: CYP2D6 to oxymorphone CYP3A4 to noroxycodone ketoreductase <sup>113</sup>	<u>↓ levels oxymorphone</u> Inhibition of 2D6 3A4 induction (less substrate for 2D6 pathway)  <u>↑ oxymorphone levels</u> 3A4 inhibition (shunting to 2D6 pathway)	Possible opiate withdrawal and loss of analgesia, although ↓ oxymorphone levels does not appear to alter pharmacodynamics of oxycodone. Possible opiate toxicity.	Monitor for signs/symptoms of opiate withdrawal (see under “Meperidine”). Reassess level of analgesia.  Monitor for signs/symptoms of opiate toxicity (see under “Codeine”).

**Table 5. Interactions between antiretrovirals and benzodiazepines<sup>137-141</sup>**

Reference	Study type	Patient(s)	Nature of interaction	Recommendation
<b>Alprazolam</b>				
Frye et al.(1997) <sup>137</sup>	Pharmacokinetics of 1.0 mg alprazolam determined prior to ritonavir treatment and following twelve days of escalating ritonavir doses.	Healthy volunteers	AUC of alprazolam ↓ 12%. Ritonavir did not produce clinically important impairment, and had no effect on peak sedation. Combination did appear to prolong sedation.	<b>Short-term PI administration:</b> Monitor for alprazolam toxicity (e.g., sedation, dizziness, ataxia, respiratory depression) with acute administration of ritonavir, and possibly other PI's and delavirdine.  <b>Chronic ritonavir administration:</b> Monitor for alprazolam withdrawal (e.g., anxiety, dysphoria, nausea, muscle twitching, insomnia, panic/paranoia, convulsions) and loss of anxiolysis with chronic ritonavir use.
Greenblatt et al.(2000) <sup>138</sup>	Double-blind, randomized 2-way cross over study of pharmacokinetics of 1.0 mg alprazolam with ritonavir or with placebo.	10 healthy volunteers.	Alprazolam half-life ↑ from mean of 13 hours to mean of 30 hours (p < 0.005). Alprazolam clearance ↓ to 41% of control values with ritonavir (p < 0.001). Ritonavir ↑ benzodiazepine agonist effects such as sedation and performance impairment.	

Reference	Study type	Patient(s)	Nature of interaction	Recommendation
<b>Midazolam</b>				
Palkama et al.(1999) <sup>139</sup>	Randomized, double blind, cross over study. Patients received treatment with saquinavir-sgc 1200 mg or placebo three times a day for 5 days. On day 3, received either 7.5 mg midazolam by mouth or 0.05 mg/kg midazolam IV over 2 minutes. On day 5, second dose of midazolam given, alternating routes of administration.	12 healthy volunteers.	<p>Oral midazolam: Saquinavir ↑ C<sub>max</sub> 2.3 fold (p &lt; 0.001), ↑ AUC 5-fold (p &lt; 0.01), ↑ half-life from 4.3 hours to 10.9 hours (p &lt; 0.01) and ↑ bioavailability from 41% to 90% (p &lt; 0.001). Sedative effects of oral midazolam profoundly enhanced.</p> <p>IV midazolam: Saquinavir ↓ clearance by 56% (p &lt; 0.001) and ↑ half life from 4.1 to 9.5 hours (p &lt; 0.001). Authors suggest ↓ initial midazolam dose by 50% when given by infusion, followed by careful titration.</p>	Midazolam contraindicated with PI's, delavirdine and efavirenz. If necessary to use combination, consider dose ↓ of 50% with careful titration and monitoring for toxicity (e.g., extreme/prolonged sedation, respiratory depression, hypotension).

Reference	Study type	Patient(s)	Nature of interaction	Recommendation
Merry et al.(1997) <sup>140</sup>	Case report. Patient received 5.0 mg midazolam IV for bronchoscopy with no ill effect. Eight weeks later, patient received second 5.0 mg midazolam dose IV for bone marrow aspirate and biopsy. Between the first and second dose, patient began saquinavir-hgc based HAART regimen.	32-year-old male with advanced HIV	Following second dose, patient did not wake spontaneously and required flumazenil due to prolonged sedation, possibly as a result of an interaction with saquinavir.	
<b>Triazolam</b>				
Greenblatt et al.(2000) <sup>141</sup>	Double-blind, randomized, cross over study of pharmacokinetics of 0.125 mg triazolam concurrent with ritonavir or placebo.	6 healthy volunteers.	Ritonavir ↑ triazolam elimination half-life from 3 hours to 41 hours (p < 0.005) and ↓ triazolam clearance to 4% of control values (p < 0.005). Sedation and performance impairment	Avoid combination of triazolam and protease inhibitors, delavirdine or efavirenz.

Reference	Study type	Patient(s)	Nature of interaction	Recommendation
			magnified by ritonavir	

Key: AUC = area under the concentration-time curve, Cmax = maximum plasma concentration, HAART = highly active antiretroviral therapy, IV = intravenous, sgc = soft gel capsule



In China and Malaysia, Eastern Europe and Russia, Central Asia, and parts of Latin America, the majority of HIV infections are due to injecting drug use. Yet injection drug users and other people who use drugs often have little to no access to the HIV treatment available in these regions.

In a time when universal access to HIV treatment is a shared goal, and when growing numbers of studies indicate that people who use drugs are capable of adhering to antiretroviral therapy (ARV), why is there such inequitable access to treatment? Is it because of discrimination, lack of political attention, and community organizations not being heard? Or is it also because treatment professionals are overwhelmed by the demands already placed on them, and tend to see people who use drugs as difficult, “hopeless” patients who cause trouble and take more time?

*Delivering HIV Care and Treatment for People Who Use Drugs: Lessons from Research and Practice* seeks to address these questions by presenting information on caring for drug users with HIV, and those with HIV and other infections. Chapters that are scientific in nature are accompanied by analyses and case studies highlighting the politics and policies influencing the provision of HIV treatment to drug users.

Key issues examined by *Delivering HIV Care and Treatment for People Who Use Drugs* include:

- ▶ Measures to support HIV treatment adherence, including opiate substitution therapies and directly administered antiretroviral treatment
- ▶ Providing HIV treatment in prison settings
- ▶ Treating HIV and coinfections such as viral hepatitis and tuberculosis
- ▶ ARV and interactions with street drugs and medications used in drug treatment
- ▶ Ethical and practical considerations for including drug users in HIV treatment and prevention research

The marginalization and discrimination faced by drug users has had terrible public health consequences. *Delivering HIV Care and Treatment for People Who Use Drugs* provides a strong message to researchers, medical care providers, public health officials, HIV/AIDS activists, and the pharmaceutical industry that drug users are deserving and capable patients who must not be isolated or ignored.

